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Editorial

Mechanism of Pain in Peptic Ulcer: A Reply

IN a recent editorial in this Journal[1] Dr. Arthur Bloomfield analyzes the "pros and cons of the acid irritation versus the spasm" theories of the mechanism of pain in peptic ulcer, cites the conclusion of Ruffin, Baylin, Legerton and Texter[2] that "abnormal motility is the fundamental mechanism through which ulcer pain is produced," presents arguments in support of this view, and suggests that it will be necessary "to await rebuttal of these observations by the advocates of the acid-irritation theory." A good opportunity thus arises to examine the evidence.

The acid irritation group holds that a painful ulcer is a sensitive lesion whereas the other group contends that the ulcer is insensitive and that "spasm or at least some disturbance of motility perhaps in the pyloric region is the cause" of the pain. "One must, of course, assume," says Dr. Bloomfield, "that the spasm of ulcer indigestion is not normal motility, that there is some sort of dyskinesia, some conflict of waves, to produce these symptoms." The acid irritation group asks what spasm, what sort of dyskinesia and what conflict of waves? There is, says this group, no direct evidence to support the assumption that the pain must be produced in some vague way by spasm, "some sort of dyskinesia, some sort of waves." On the other hand, there is abundant direct evidence to show that a painful ulcer is a very sensitive lesion, that acid gastric juice on the surface of such an ulcer is the usual stimulus for the production of pain, and that mechanical stimuli such as peristalsis and spasm at the site of a sensitive ulcer may evoke pain. But what are the arguments made by Dr. Bloomfield?

EVIDENCE AGAINST ACID IRRITATION THEORY

The first point of evidence listed against the acid irritation theory is that many ulcers run their entire course without pain even though bathed with acid. The deduction drawn from this fact is indeed a non sequitur. The fallacy may be indicated by the comparable argument that since many corns on the feet are painless in spite of pressure from shoes, corns are therefore not due to pressure. Painless ulcers are simply those in which the product of ulcer sensitivity multiplied by concentration of acid multiplied by time does not evoke a sufficient number of pain impulses to break through the cerebral barrier into consciousness and be recognized as pain.

Dr. Bloomfield's second point is that identical symptoms occur in patients who have no ulcer. In presenting this argument he shows a tendency to equate symptoms with ulcer. It is a well known clinical fact that one cannot differentiate the various causes of abdominal pain simply by the *quality* of the sensation or by its location in the abdomen. Experimentally I observed in 1925[3] (pp. 124, 126) that distention of a balloon in the intestine in certain patients with active ulcer and in others with healed ulcer produced pain at times indistinguishable from the patient's typical distress; in one patient pain of this type was produced after resection of the ulcer. The experiments were interpreted "to indicate a poor power of localization and differentiation of distress arising from different but adjacent portions of the intestine and produced in different ways." It certainly cannot be contended that if gallstones, peptic ulcer and distention of a balloon in the intestine all produce identical pain, or at

least pain so interpreted by the patient, the mechanism of the pain is the same in all three instances.

Dr. Bloomfield's third point having to do with persistence of pain after excision of an ulcer may be answered in the same manner. It is not in accord with clinical experience to conclude that because pains seem identical they must be produced by the same mechanism.

Dr. Bloomfield's fourth point is that identical indigestion may be seen with high acidity, low acidity and anacidity. Here again it is clear that one cannot equate *indigestion* with *ulcer pain*, or *symptoms* with a *lesion*. It is true that ulcer pain occurs with varying degrees of acidity; the other two variable factors are the sensitivity of the lesion and time.

The fifth point has to do with the prompt relief of symptoms on rest, sedatives and simple diet without any change in the gastric acidity and hence the conclusion that some other mechanism is responsible, since by implication it seems to Dr. Bloomfield unlikely that the pain mechanism becomes insensitive. In fact, there may very well be, with the regimen mentioned, a decrease in the *acidity* (i.e., the hydrogen ion concentration) on the surface of the ulcer resulting not only in a decrease in the stimulus but also a rapid decrease in the inflammation, edema and sensitivity of the lesion. These factors could readily account for the relief in pain.

In his sixth argument Dr. Bloomfield cites the reproduction of the pain of duodenal ulcer by inflation of a small balloon in the duodenum by Jones[4] as "incontrovertible evidence that distention of muscle, spasm or altered motility can produce indigestion symptoms." To the best of my knowledge no one has ever questioned this fact. Dr. Bloomfield then states that "those in favor of the acid irritation theory ask how one can get a burning pain without acid?" "The syllogism," says he, "seems obvious: the pain is burning in character; acid burns; therefore the pain must be produced by acid." It is difficult to realize that such superficial reasoning is seriously ascribed to the adherents of the acid irritation theory. Knowledge that "heartburn" and burning epigastric distress may occur in patients with complete achlorhydria, as in pernicious anemia, is so old in my own clinical experience that I cannot trace its origin except to credit it to my teachers in the "Sippy School" in the early twenties. However, this has nothing to do with the mechanism of pain in peptic ulcer.

The seventh point referring to the gastroscopic observation of pain synchronous with violent contractions of the pylorus is not pertinent, even if it is valid. Dragstedt and I[3] observed at operation under local anesthesia on a man with an acutely sensitive *duodenal* ulcer that spasm of the duodenum at the site of the ulcer produced the patient's typical severe cramping pain although peristaltic waves of the gastric antrum were painless. The injection of hydrochloric acid solution into the duodenum likewise produced pain whereas the injection of a solution of sodium bicarbonate relieved the pain. Violent contractions of the stomach or pylorus may indeed produce pain if the lesion is sufficiently sensitive, as was shown in 1927.[3]

EVIDENCE FOR THE ACID IRRITATION THEORY

As Dr. Bloomfield lists the evidence *for* the acid irritation theory, his own strong convictions lead him promptly to destroy it. He first mentions the relief of pain with alkali or food and then objects that relief occurs with amounts too small to neutralize all the acid and that it often coincides with belching. On innumerable occasions over the years my colleagues and students, as well as investigators in other clinics, have produced ulcer distress by injecting acid solutions through a gastric tube with no change in intragastric tension; similarly the removal of the acid or neutralization by the injection of an alkaline solution has afforded relief without changes in intragastric tension and without belching.[3,8,9,18] Protocols and kymographic tracings are available in numerous papers.[10,11,14] Relief of pain with only a few swallows of anything is not difficult to understand in duodenal ulcer because the act of swallowing temporarily inhibits gastric motility and gastric emptying; acid present on the surface of the ulcer is immediately neutralized by the reflux into the bulb of alkaline duodenal content.

Dr. Bloomfield concedes that the aspiration of acid juice may relieve pain, but he contends that it also "could readily alter a state of abnormal tonus or spasm." No evidence is presented. "It is obvious," says Dr. Bloomfield, "that the last film of acid covering an ulcer cannot be removed. It would seem to make little difference whether the ulcer is irritated by a 1 mm. layer of tenth normal acid or whether it lies at the bottom of a big lake of juice. All this is very much like trying to measure the depth of the ocean with a foot

rule." Is this true? I think not. It would be interesting to subject Dr. Bloomfield's hypothesis to the test of experiment: apply a 1 mm. layer of tenth normal hydrochloric acid to a weeping skin surface and check its hydrogen ion concentration every five minutes. The capacity of proteins to combine with hydrogen ions is phenomenal.

The third consideration refers to the fact that the injection of acid does not always produce pain and suggests that "the procedure of injection could perhaps produce a disturbance of motility as well as acid irritation." But does it? The reader is referred to the negative kymographic and roentgenologic evidence cited.

The fourth point, deriving from the fact that the administration of steroids may stimulate gastric secretion and thus activate an ulcer, is interpreted by Dr. Bloomfield as evidence against the acid irritation theory because so many of these ulcers are painless and are discovered only by the presence of a complication or by x-ray. This is simply a restatement of the question of the painless ulcer already discussed.

ABNORMAL MOTILITY

Since both Dr. Bloomfield and Dr. Ruffin emphasize the role of "abnormal motility," it will be necessary to discuss this problem in considerable detail. It is of interest to note that Dr. Ruffin[2] in the paper mentioned by Dr. Bloomfield began his closing remarks as follows: "I agree entirely with Dr. Palmer that hydrochloric acid is the usual stimulus in the production of ulcer pain. I disagree with him, however, on the role of motility." Apparently Ruffin considered that acid is the usual stimulus for pain, but that changes in motility are necessary for its mediation. It is regrettable that he and his co-workers did not present kymographic tracings or x-ray pictures of such motility changes. One film shows a well filled duodenal bulb with acid barium in the crater, and no pain; the second shows an active gastric antrum, a deformed bulb, and acid barium in an ulcer crater "with simultaneous relief of pain"; the third plate with four views of a gastric antrum and duodenal bulb following the intramuscular injection of banthine® is described as "arrested motility and relief of pain." No spasm or abnormal motility causing pain is shown. It is not permissible to conclude that unarrested or abnormal motility produces pain simply because "arrested motility" was noted with "relief of pain." In another paper by the same authors[6] there are shown two x-ray views of the stomach with and without pain. There is no discernible difference in motility or spasm in the views with and without pain. It is noteworthy that in Figure 1, page 313, in which a deformed bulb is shown with acid barium in the ulcer crater, antral motility *during pain* is minimal and the pylorus is open. In the stomach with a gastric ulcer (Fig. 2, p. 314) shown with and without pain, there are no areas of spasm or hypermotility to account for the pain. In both papers the authors simply state that roentgenographic observations disclosed the presence of "abnormal motility patterns" but they do not give graphic evidence of these patterns or of the changes seen; they do not show evidence of pylorospasm, gastrospasm or increased intragastric tension correlated with pain. Dr. Bloomfield did not refer to another paper by Hightower and Gambill,[7] presented at the same time, based on a study of twelve patients with duodenal ulcer. Conclusions similar to those of Ruffin et al. were reached, although in the only tracing published it is apparent that the pain correlated only partially with the antral contractions and continued for at least a few minutes after the motility ceased.

None of these authors present evidence to contradict the pictures presented in 1927;[3] on page 123 there is shown the film of a patient with a duodenal ulcer *during pain* with an open pylorus and a well filled bulb; on the same page there are to be seen views of a stomach containing an active gastric ulcer, an open pylorus with a well filled bulb and a gastric antrum *without* hypermotility during the presence of pain. Kymographic studies in the same article (p. 127) clearly show that the presence and absence of pain cannot be correlated with intragastric or, indeed, with intraduodenal pressure. In subsequent publications these studies were confirmed and documented with further illustrations.[8,9] In 1946 they were completely confirmed, extended and further documented in two superb papers by Bonney and Pickering.[10] Further confirmation has come in more recent years.[9,12] The only tracing published by Hightower et al. is reminiscent of certain ones published in 1927[3] (pages 115, 116, 121) in which production of pain by the peristaltic waves was shown to be dependent upon the presence of adequate amounts of hydrochloric acid. Similar contraction waves were recorded *without pain* after con-

tinued desensitization of the mechanism by means of antacid therapy.

It is regrettable that Dr. Bloomfield did not mention the work of Rowlands and Friedlander,[11] published in 1952, containing eight illustrative figures of kymographic tracings made with the balloon in the stomach or duodenum in patients before, during and after the appearance of ulcer pain. The well presented data clearly led to conclusions, in part, as follows: "No evidence was obtained that ulcer pain was associated with an increase in 'tone' or of short or sustained contractions of duodenum or stomach. Hexamethonium bromide has been shown to reduce 'tone' and to inhibit contraction waves in stomach and duodenum, an effect independent of postural hypotension or fainting. . . . Patients obtained no relief from ulcer pain when all contractions were abolished and 'tone' of the gut was reduced, by hexamethonium. . . . It is concluded that the attacks of pain associated with uncomplicated peptic ulcer are not caused by muscular contractions or by increased tension in the stomach or duodenum."

Dr. Bloomfield likewise did not refer to a somewhat similar paper by Palmer, Vansteenhuyse and Kirsner[12] in which, in twenty-three of twenty-six experiments carried out in eighteen patients, an acid test performed before and after administration of an anticholinergic compound produced pain, proving thereby that the compound did not desensitize the pain mechanism.

These results were to be expected because of the earlier demonstration by Dragstedt, Woodward, Harper and Storer[13] that not even surgical vagotomy abolishes the positive response to the acid test in patients with a sensitive ulcer.

A more recent paper by Woodward and Schapiro,[14] published after Dr. Bloomfield had written his editorial, presents tracings of duodenal motility inhibited by antrenyl® given intravenously, with no effect upon the pain of a duodenal ulcer. The authors conclude that in four of seven patients with duodenal ulcer, pain "was produced by the intraduodenal administration of N/10 HCl at a rate which lowered the duodenal pH to 1.88 or less. The onset of ulcer pain was not associated with any change in duodenal motility. Ulcer pain induced by intraduodenal hydrochloric acid was not relieved by anticholinergic drugs, even though duodenal motility was abolished."

Thus there is abundant evidence to refute the concept that ulcer pain results from "abnormal motility," that it is mediated only by muscular tension.

THE SITE OF ORIGIN OF THE PAIN

Basically, the concept which the opponents of the acid-irritation theory seem most unable to accept is that ulcer pain arises in the lesion itself without the mediation of muscle tension. Perhaps the basis for this hesitation is the old and oft-repeated observation that the cutting, pinching and tearing of normal viscera in the unanesthetized animal or human does not produce pain whereas smooth muscle spasm or distention of smooth muscle may do so. This leads to the question as to whether or not visceral pain is fundamentally different from somatic pain. Nerves capable of transmitting painful sensations are present in the viscera in large numbers. The problem divides into two factors: the level of the threshold for visceral pain and the nature of an adequate stimulus. Vasodilation and tissue injury have been shown experimentally by Bilisoly, Goodell and Wolff[15] to lower the somatic pain threshold. There is good evidence that inflammation can lower the visceral pain threshold in a similar manner. This point is central to the entire discussion because if the pain threshold in the ulcer can be lowered so that mechanical, thermal or chemical stimuli can be painful there need be no hesitation in accepting the concept of acid irritation of nerve endings and hence no reason to seek spasm or "abnormal motility" as the mechanism by which ulcer pain is mediated. Whitlow[16] observed many years ago that inflammation may lower the visceral pain threshold. Wolf and Wolff[17] applied mustard to an area of exposed gastric mucosa, keeping another area as a control, and from time to time subjected the two areas to stimulation. When the mustard-treated side was "intensely red, boggy and edematous . . . intense pain occurred with application of the stimuli" whereas no pain occurred when the stimuli were applied to the control area. Bently[18] likewise noted in studies on visceral pain in patients subjected to operation under local anesthesia that "the exposed ulcerated stomach or duodenum was sensitive to pressure, to pin prick, and to chemical stimulation. The non-ulcerated stomach wall was insensitive to the stimuli." Thus the evidence that an inflammatory process, such as an ulcer, can lower the visceral pain threshold and increase the sensitivity is indisputable; ulcer pain

can arise in the lesion itself by direct stimulation of the ulcer; local or remote spasm or muscular tension need not be hypothesized.

NATURE OF THE STIMULUS

The evidence that acid gastric juice is the usual stimulus to the pain mechanism seems conclusive;[3,5,8,9,10,12,13,14,19,20] the questions raised have really revolved about the site of origin of the pain and the roles of abnormal motility or muscular tension in its mediation. There have been misunderstandings by those who expect a hairspring mechanism. Thus Ruffin and his associates[2,6] presented x-ray evidence of acid barium in the crater of a duodenal ulcer with no pain or with relief of pain and considered this fact to be hard to reconcile with the acid irritation theory. It is not so at all. Barium sulfate sediments rapidly. The barium itself is not irritating; the irritating element is the acid in the supernatant fluid. Barium sulfate and oozing serum could rapidly protect the raw surface from the hydrogen ions. The more remarkable phenomenon to my mind is the production of pain by this method rather than the failure to do so. No one has contended that the contact of acid with a raw surface immediately and invariably evokes pain. There seem to be at least three variables in the process: (1) The pain threshold in the nerve endings; (2) the concentration of acid in immediate contact with them, and (3) time. The reader is referred again to the classical work of Bonney and Pickering[10] with respect to somatic pain. Reference to the work of Wolf and Wolff[17] and of Bentley[18] strongly suggests, in fact proves, I think, that visceral pain thresholds are influenced similarly. Thus the ulcer produced by the digestive action of acid gastric juice, when once the mucosal barrier has in some manner been broken down, is accompanied by a chemical inflammation which in turn lowers the visceral pain threshold. In such a situation acid gastric juice of varying concentrations acts upon the nerve endings for variable periods of time and evokes pain of varying intensity;[19] mechanical stimuli also may evoke pain;[3] however, with desensitization, due presumably to decrease in the inflammation, the pain threshold rises and peristaltic activity of equal intensity then becomes painless.[3]

SUMMARY

There is, of course, much more that could be said on this subject and much additional evidence that could be cited but this editorial is already too long. Thirty years ago the concept current in physiologic and clinical circles was that, like the hunger pang, ulcer pain arose from gastric contractions. Gastric acidity was thought to play no role in the pathogenesis of peptic ulcer or in the mechanism of pain. Sippy alone dissented, writing, "it is practically certain that free hydrochloric acid is the important element in the irritant. . . . Distress attributable to uncomplicated ulcer is found only when the fluids of the stomach contain free hydrochloric acid in adequate concentration."[20] The passing years have proved the validity of his observations. It is clear that peptic ulcers are indeed "peptic" ulcers, that they arise from the digestive action of acid gastric juice, that inflammation (chemical) lowers the pain threshold so that the normally insensitive bowel becomes sensitive, that the pain arises in the ulcer itself, that the usual stimulus for pain is the acid gastric juice, and that in a tender lesion mechanical stimuli such as spasm, peristalsis, touching or pinching may evoke pain. Much of the seeming mystery of visceral pain dissolves when the significance of the lowered pain threshold is fully comprehended.

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Clinical Studies

Quantitative Study of Intrapulmonary Gas Mixing in Emhhysema*

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Uneven mixing of gas within the lungs is characteristic of pulmonary emphysema. A number of technics have been devised to demonstrate unequal gas mixing in emphysema and to grade the severity of the defect. These have depended upon measuring various consequences of impaired mixing, such as delay in washing a test gas out of the lungs, delay in introducing a test gas into the lungs, or abnormally great variation in the concentration of expired gas during the course of a single breath.

Recently it has become possible to describe defective intrapulmonary gas mixing in more complete terms. This has resulted from the finding that an unevenly ventilated lung behaves as if it consisted of several subdivisions, each evenly ventilated at its own rate.[1,2] The volume and ventilation rate of these subdivisions can be measured, and these measurements provide a simple quantitative picture of the defect in intrapulmonary gas mixing. Description of the entire lung in this way requires elaborate analytical apparatus which can follow rapidly changing gas concentrations. However, the large, slowly ventilated lung spaces which occur when intrapulmonary mixing is grossly impaired can be measured by relatively simple means.[3,4]

By these technics very large lung volumes with very slow ventilation rates have been found in patients with severe pulmonary emphysema. When full account of these slow spaces is taken in calculating the conventional subdivisions of lung volume, unusually great values for functional residual capacity are obtained in some patients with advanced emphysema.[4] It is the purpose of this report to describe the extent of the mixing defect in a large series of patients with pulmonary emphysema. The conventional measurements of maximum breathing capacity and the ratio of residual to total lung capacity have also been made to determine how closely abnormalities in these values may be related to each other.

Methods and Subjects

The method for measuring functional residual capacity and the size and ventilation rate of poorly ventilated subdivisions of the lung has been described in detail elsewhere.[4] An "open-circuit" system is used. The subject first breathes a 50 per cent oxygen—50 per cent helium mixture for fifteen minutes to introduce helium into the lungs. He is then switched to tank oxygen and the expired gas is collected for measurement of volume and helium concentration. After one to two minutes of this "wash-out" period the helium concentration in the expired air usually reaches 3 per cent, even in emphysematous subjects, and thereafter the helium concentration is followed continuously by a sensitive katharometer until it reaches 0.05 per cent, when the analysis is abandoned. By graphic analysis of the plot on semi-logarithmic paper of helium concentration against time, the volume (V_s) and ventilation rate ($\dot{V}_s$) of the most poorly ventilated lung subdivision can be estimated. (Fig. 1.) In some cases the analysis can be extended to the next poorest ventilated space. From the volume and helium concentration of the pooled expired gas the functional residual

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capacity (FRC) is calculated, as in other open-circuit methods for measurement of FRC. It is a special advantage of the present method that corrections of the FRC for incomplete filling of the lungs with helium during the equilibration period and incomplete emptying during the washout period can be derived from the washout curve. These corrections may be very large when intrapulmonary gas mixing is grossly uneven. The vital capacity and expiratory reserve volume are measured as usual. The residual capacity (RC) and total capacity (TC) are calculated from these values and from the FRC. The maximum breathing capacity (MBC) is determined by conventional means.[5]

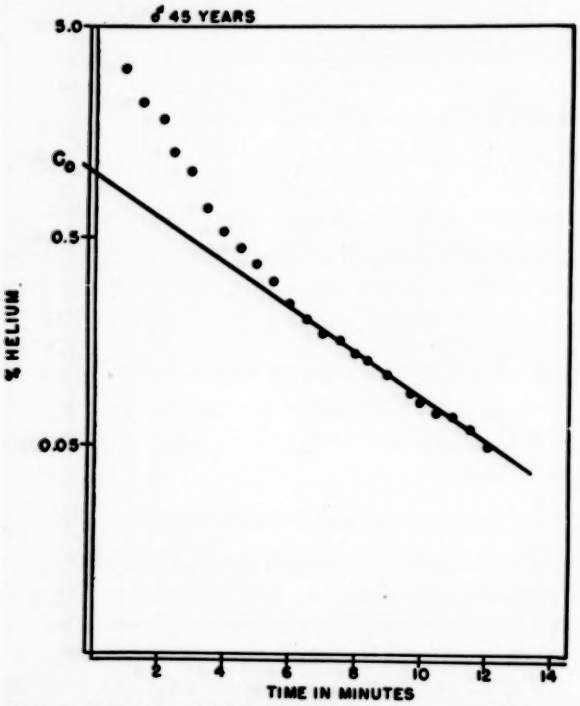

FIG. 1. Helium washout curve of a patient with moderate pulmonary emphysema. The last part of the curve falls along a straight line. This indicates that helium is being excreted at this time from what is, in effect, a single slowly but uniformly ventilated space. This space is uncovered when the more rapidly ventilated parts of the lung have been washed out. Its presumed washout line during the early part of the period is constructed by extrapolating the straight line until it intersects the ordinate (at C_0). The line relates concentration, C (in per cent helium), to time, t (in minutes), where C is the contribution of this slowest ventilated lung space to the total helium concentration in the general expired air. The equation of the line is: $C = C_0e^{-kt}$, where k is the ratio between ventilation rate and volume of the slow space $\frac{\dot{V}s}{Vs}$. The equation is solved for k by using values of C and t for any two points on the actual line. The ventilation rate of the slow space, $\dot{V}s$, is obtained from the relation $\frac{\dot{V}s}{\dot{V}t} = \frac{C_0}{50}$, where $\dot{V}t$ is the subject's total minute ventilation and 50 is the initial concentration of helium throughout the lung. Knowing $\dot{V}s$ and k, the size of the slow space, Vs, is calculated from the relation $\frac{\dot{V}s}{Vs} = k$.

Observations were made on sixty-three patients with pulmonary emphysema. The diagnosis of emphysema was based on clinical and roentgenologic findings. The severity of the disease ranged from slight to far advanced. Of these patients eighteen also had definite bronchial asthma but were not studied during an obvious attack. The age range of the entire group was twenty-five to seventy-one years. Fifty-six were males. All but a few were hospital in-patients, and all were undergoing conventional treatment including the use of antibiotics and bronchodilators.

RESULTS

The information obtained from the sixty-three patients is detailed in Table 1.

Uneven Intrapulmonary Mixing in Emphysema. The basic data relating to uneven mixing in each subject are the size, Vs, of the most poorly ventilated lung region and its "turnover rate," k_s. The turnover rate is the ratio between minute ventilation and volume of the region. As an example, a space of 2,000 ml. with a ventilation rate of 200 ml. per minute has a "k" of 0.1. For comparison with the values of k_s in Table 1 it is useful to recall that k for the lung as a whole, or the ratio between total minute ventilation and FRC, is normally in the general range of 2.0. For judging the extent of impairment of gas mixing it is convenient to express the volume of the worst ventilated space, Vs, as a fraction, "f," of the FRC. The values of f and k_s describe the relative size and ventilation rate of the most poorly ventilated region of the lung. The distribution of f and k_s in the present patients and in twenty-eight normal persons is shown in Figure 2. There is much scatter but a typical emphysematous patient might well have half of his resting lung volume ventilated at a tenth (k = 0.2) of the normal over-all ventilation rate. Many of the patients have very large lung subdivisions, or "slow spaces," which are almost unventilated.

Stability of the Slow Subdivision. As a rule, the slow space in normal persons and in patients with advanced emphysema changes relatively little over a period of days or weeks. Figure 3 summarizes the results of five measurements of

TABLE 1

No.	Initials	Age	Sex	Surface Area (M^2)	Vital Capacity (L.)	Maximum Breathing Capacity (L./min.)	Functional Residual Capacity (FRC) (L.)	Residual Capacity (RC) (L.)	Total Capacity (TC) (L.)	RC/TC × 100	Total Ventilation Rate ($\dot{V}_T$) (L./min.)	Volume of Slow Space (V_S)[1] (L.)	Ks
1	W. W.	48	M	1.76	2.61	20.4	6.69	6.19	8.80	70	5.7	4.75	.10
2	A. F.	71	M	....	1.41	22.1	6.11	5.40	6.81	78	11.8	5.90	.19
3	G. D.	64	M	1.43	2.12	37.7	4.42	3.38	5.50	61	10.7	2.18	.20
4	J. D.	68	M	1.78	2.30	24.7	3.86	2.80	5.10	55	13.4	2.68	.29
5	J. C.	65	M	1.92	2.97	24.7	6.37	4.65	7.62	61	14.3	3.48	.05
6	W. B.	55	M	1.84	2.90	62.5	4.71	3.37	6.27	54	17.0	1.70	.14
7	W. S.	68	M	1.84	2.59	26.0	4.74	3.99	6.58	61	15.2	1.00	.18
8	C. L.	61	M	2.08	2.82	78.0	3.97	3.25	6.07	54	12.4	1.10	.20
9	O. W.	50	M	1.94	3.22	53.3	4.66	3.19	6.41	50	10.0	1.96	.40
10	L. Y.	60	M	1.51	3.30	52.0	4.98	3.67	6.97	53	19.7	2.56	.77
11	J. S.	58	M	1.52	2.41	39.0	3.44	2.46	4.87	51	8.7	2.72	.21
12	R. S.	69	M	1.82	2.16	36.8	5.06	4.41	6.57	67	11.5	2.30	.22
13	L. R.	40	M	2.04	....	.....	5.42	....	....	..	13.1	1.43	.22
14	W. R.	46	M	1.78	3.88	49.4	5.84	3.99	7.87	51	14.9	2.42	.53
15	A. P.	69	M	1.56	2.41	23.4	7.01	6.10	8.51	72	17.3	4.20	.12
16	D. O.	55	M	1.81	1.94	27.3	5.94	5.21	7.15	73	13.3	2.46	.07
17	G. M.	47	M	1.82	2.74	31.2	5.69	4.42	7.16	62	10.0	1.46	.23
18	J. McD.	64	M	1.88	1.70	20.8	4.39	3.71	5.41	69	10.3	1.76	.11
19	W. M.	55	M	1.93	1.58	27.3	4.63	4.01	5.59	72	14.6	2.47	.27
20	W. G.	50	M	....	....	.....	4.13	....	....	..	11.7	0.96	.26
21	R. R.	47	M	1.99	3.34	31.2	5.46	4.51	7.85	57	8.8	3.60	.13
22	E. L.	57	M	....	2.98	67.6	4.64	3.11	6.09	51	17.9	2.12	.50
23	R. K.	63	M	1.70	2.82	22.1	8.07	6.41	9.23	70	15.9	6.50	.23
24	H. B.	30	M	1.67	2.45	39.0	6.25	5.34	7.79	69	12.1	4.45	.06
25	J. A.	52	M	2.02	3.07	31.2	5.88	4.78	7.85	61	16.9	2.56	.12
26	L. S.	66	M	1.80	2.39	33.8	6.33	5.19	8.56	60	14.3	3.65	.20
27	G. K.	65	M	1.68	2.59	42.9	3.77	2.57	5.16	50	14.4	2.13	.21
28	B. M.	50	M	1.92	2.69	40.0	6.67	....	....	..	13.2	4.10	.20
29	E. S.	56	M	1.88	3.22	58.8	3.72	2.65	5.87	45	13.0	1.63	.51
30	G. T.	66	M	1.94	2.84	40.0	5.43	4.31	7.15	60	13.3	3.47	.46
31	G. H.	61	M	1.45	1.58	20.8	6.90	6.05	7.63	77	9.5	5.30	.14
32	F. S.	55	F	1.50	2.78	41.2	3.84	2.84	5.62	51	11.1	2.55	.41
33	C. B.	67	M	1.48	3.38	56.0	4.63	2.64	6.02	42	14.5	4.37	.63
34	R. S. C.	59	M	1.96	5.02	70.2	4.45	2.35	7.37	32	15.5	3.87	.60
35	B. J.	53	M	1.74	2.75	39.0	4.17	2.57	5.32	48	12.0	....	.42
36	H. S.	55	M	1.83	3.83	84.0	5.97	4.11	7.94	51	11.3	3.10	.36
37	J. B.	60	M	1.84	2.26	23.2	7.23	6.42	8.68	74	13.7	3.80	.13
38	C. W.	57	M	1.64	1.98	.....	3.93	3.20	6.26	51	7.9	2.73	.12

TABLE 1 (*Continued*)

No.	Initials	Age	Sex	Surface Area (M^2)	Vital Capacity (L.)	Maximum Breathing Capacity (L./min.)	Functional Residual Capacity (FRC) (L.)	Residual Capacity (RC) (L.)	Total Capacity (TC) (L.)	RC/TC × 100	Total Ventilation Rate ($\dot{V}_T$) (L./min.)	Volume of Slow Space (V_S)[1] (L.)	K_S
39	R. H.	51	M	1.82	2.34	29.8	5.12	4.50	6.84	66	11.8	1.77	.17
40	E. B.	47	M	1.74	2.11	33.8	5.48	4.67	6.78	69	13.0	3.46	.17
41	E. A.	48	M	2.04	2.60	37.6	7.86	6.31	8.91	71	19.9	2.30	.11
42	M. W.	52	M	1.53	2.12	32.5	4.70	4.20	6.32	67	17.1	2.40	.22
43	L. O.	50	M	2.10	4.48	87.0	4.29	2.80	7.28	38	11.8	1.43	.37
44	J. S.	45	M	1.62	3.50	85.8	4.96	3.24	6.74	48	16.4	1.64	.22
45	A. N.	66	M	1.51	3.09	72.6	5.01	3.39	6.48	52	12.1	3.93	.40
46*	M. C.	25	F	1.48	2.37	33.2	3.85	2.83	5.20	54	13.3	4.10	.63
47*	A. H.	43	F	1.65	1.39	16.9	2.63	2.17	3.56	61	9.4	2.04	.32
48*	R. J.	32	F	1.53	2.70	83.3	3.61	2.74	5.44	51	11.1	1.93	.07
49*	G. J.	41	M	1.82	3.34	52.0	3.64	2.60	5.94	44	14.8	2.89	.87
50*	R. M.	33	M	1.88	4.60	59.8	5.93	4.50	9.10	49	10.7	2.88	.12
51*	F. P.	34	M	1.72	3.97	41.6	5.07	3.16	7.13	44	16.5	1.33	.26
52*	W. P.	35	M	1.75	3.28	66.4	2.95	1.96	5.24	37	11.3	1.87	.23
53*	L. S.	41	F	1.65	3.66	71.5	3.36	2.09	5.75	36	14.7	1.27	.60
54*	V. W.	24	M	1.65	4.61	113.0	4.37	2.44	7.05	35	13.8	1.12	.33
55*	J. B.	28	M	1.97	2.32	50.0	5.27	4.27	6.59	65	12.4	0.85	.17
56*	B. S.	49	M	1.82	3.13	32.5	5.48	4.20	7.33	57	16.1	1.91	.15
57*	A. T.	57	M	1.64	3.11	19.5	5.49	4.33	7.44	58	10.5	2.78	.13
58*	K. B.	37	M	1.52	2.51	59.8	4.23	3.30	5.81	57	10.4	2.60	.13
59*	M. W.	50	F	1.48	2.90	46.8	3.04	2.69	5.59	48	8.9	2.97	.33
60*	M. W.	34	F	1.56	2.49	33.8	3.35	2.27	4.78	48	10.5	1.36	.17
61*	W. L.	43	M	1.56	1.62	18.0	7.09	6.13	7.75	79	7.7	4.23	.08
62*	J. M.	43	M	1.88	3.22	85.8	3.46	2.82	6.04	47	14.5	0.76	.19
63*	C. J.	57	M	2.10	3.78	71.5	3.67	2.92	6.70	43	11.1	1.11	.37

[1] The "slow space" is the most slowly ventilated subdivision of the lung, measured as described in the text.
* Bronchial asthma with emphysema.

the slow space and the FRC of a normal subject over a period of about two months. There are moderate changes in the slow space and the FRC during this time but the slow space remains small and well ventilated. Figures 4 and 5 illustrate the stability of the slow space in patients with advanced emphysema. Some changes are apparent, particularly in Figure 5, but the space remains very large and poorly ventilated. In contrast, patients with bronchial asthma show much variation in the slow space with variation in the severity of their asthma. Figure 6 shows the decrease in slow space and FRC of an asthmatic patient brought about by aminophylline. Similar results have been obtained in other patients with asthma, but aminophylline produces little or no reduction of the slow space in patients with advanced emphysema.

Effect of a Forced Expiration on the Slow Subdivision. The helium washout was ended in all cases when the helium concentration in the expired air had reached 0.05 per cent. At this point most of the subjects with emphysema were urged to make a prolonged, forced expiration. This usually caused a transient rise in the helium concentration of the expired air, and the maxi-

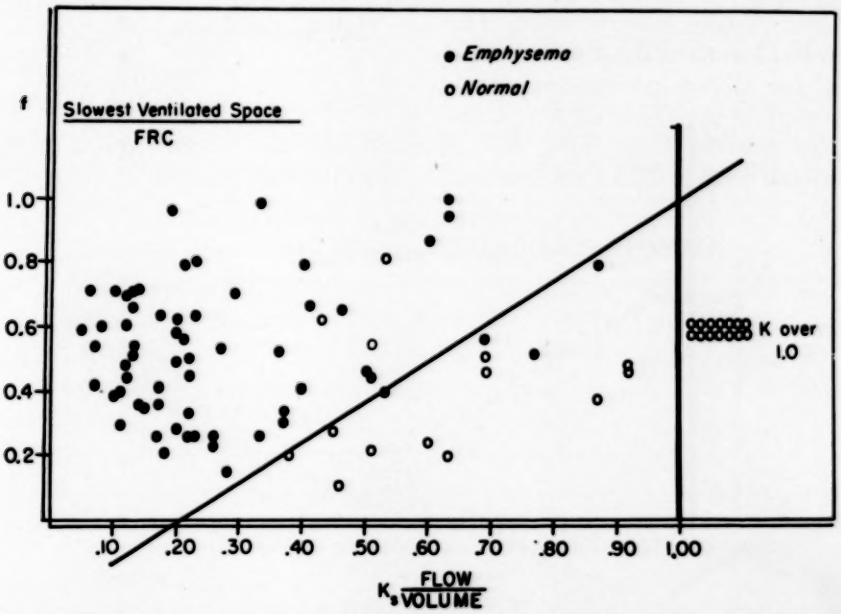

FIG. 2. The figure summarizes the characteristics of the most slowly ventilated lung space. The size of the space is expressed, on the ordinate, as a fraction of the FRC The ventilation of the slow space is expressed in terms of the turnover rate, k_s, or ratio between ventilation and volume of the slow space. In fourteen of the normal subjects the slowest space was so rapidly ventilated that it could not be measured by the present method. The diagonal line is drawn across the figure to emphasize the difference between the normal and emphysematous subjects. The three normal subjects above the line were elderly. It is evident that most of the patients with emphysema had large, poorly ventilated "slow spaces."

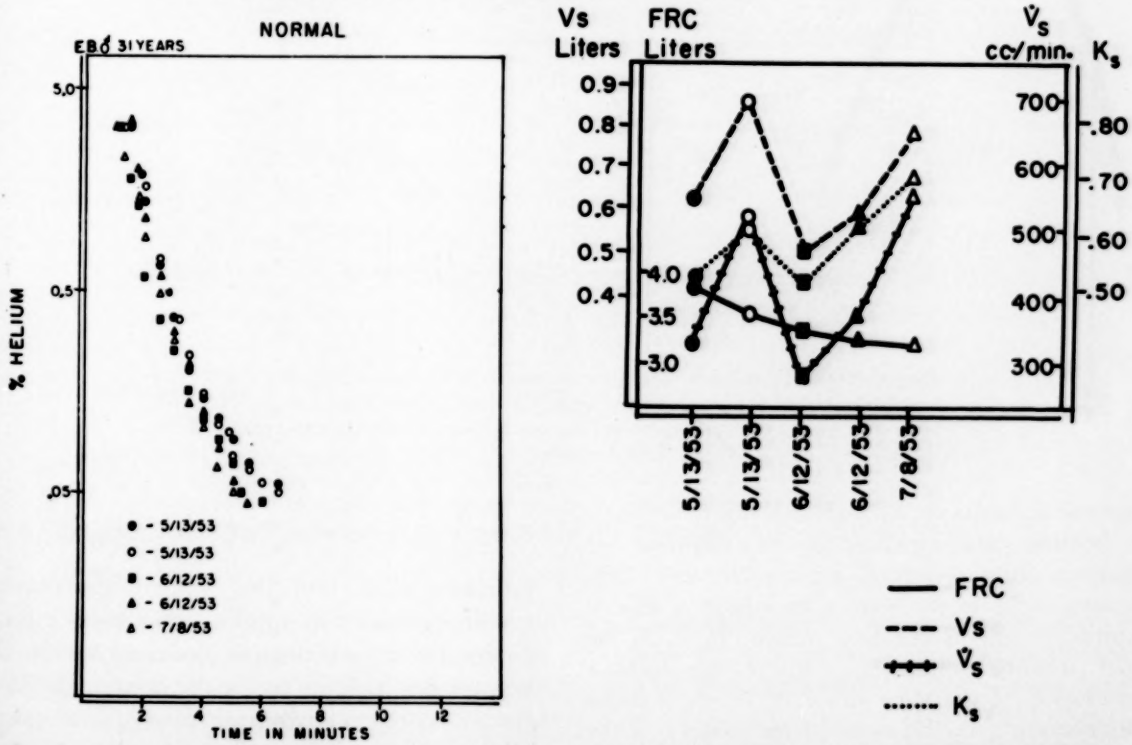

FIG. 3. Repeated helium clearance curves of a normal subject, showing persistence of a slowly ventilated lung space. The diagram at the right presents the values of functional residual capacity (FRC), volume of the slowly ventilated space (V_s), ventilation rate of this space ($\dot{V}_s$), and the turnover rate of the slow space (k_s) on each occasion.

mum katharometer reading was recorded. This value was somewhat less than the actual helium concentration of the forced expiration because the katharometer could not respond completely before subsequent breaths caused the helium concentration to fall again. The katharometer response is, however, a rough index of the change in helium concentration of the expired air resulting from a forced expiration; and this, in turn, reflects the extent to which a forced expiration affects the slow space. If $\dot{V}_t$ is the total minute ventilation, $\dot{V}_s$ is the minute ventilation of the slow space, C_t is the helium concentration in the expired air and C_s is the helium concentration in the slow space, the rate of helium excretion at the end of the washout period can be expressed as

$$\text{Helium excretion rate} = \dot{V}_t \times C_t = \dot{V}_s \times C_s$$

$$\text{and } C_t = C_s \frac{\dot{V}_s}{\dot{V}_t}$$

During the forced expiration C_s is unchanged, so that a change in C_t reflects a change in the ratio $\frac{\dot{V}_s}{\dot{V}_t}$. The increase in C_t which usually occurs indicates that the slow space contributes a greater proportion to the volume of a forced expiration than it does to a normal breath. The greater the increase in C_t, the greater the factor by which the contribution of the slow space is increased during forced expiration. Figure 7 shows the relation between the increase in katharometer reading after forced expiration

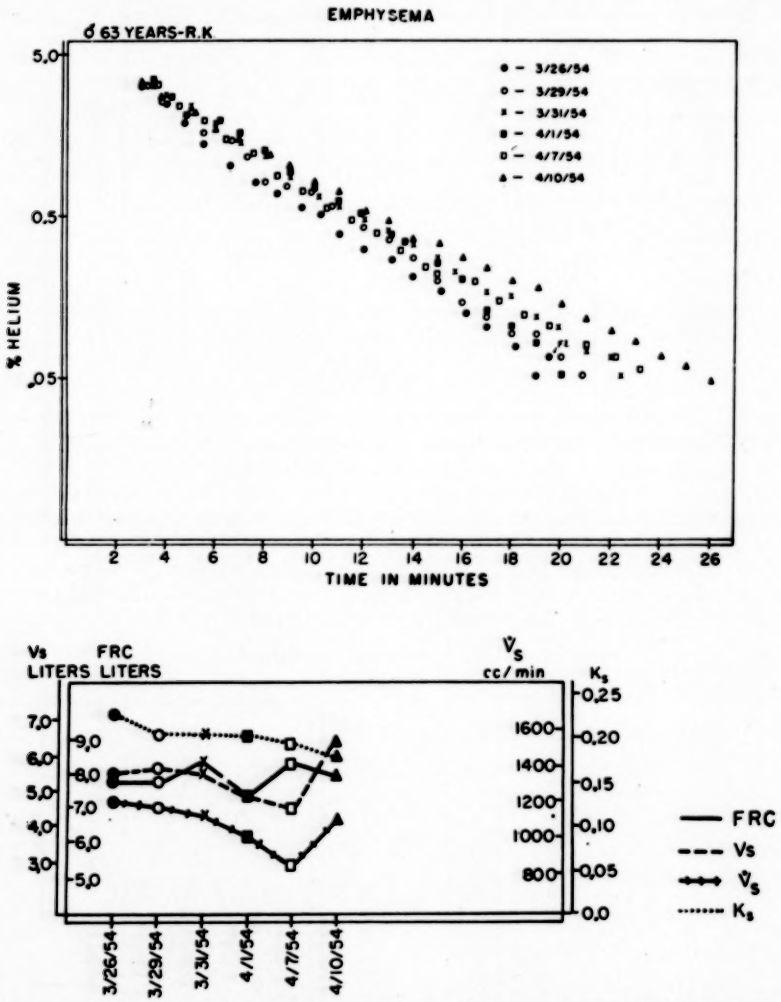

FIG. 4. Repeated helium clearance curves with measurement of the FRC and of the most slowly ventilated space in a sixty-three year old man with long-standing, severe emphysema. Treatment with antibiotics and bronchodilators produced no substantial change.

and the normal turnover rate (k_s) of the slow space in the subjects of the present study. It is apparent that the increase in helium concentration tends to be proportional to the turnover rate. That is, the slower the space, the less it is affected by a forced expiration. This is similar to the finding of Robertson[1] that the slow space in a normal subject was affected relatively less by hyperventilation than were other parts of the lung. When subjects with severe emphysema make a forced expiration, the slow space does not contribute in proportion to its volume. For this reason residual air measurements which depend in part upon alveolar air sampling are apt to underestimate lung volumes in such subjects.

Functional Residual Capacity. The spread of values obtained for the FRC is presented in Figure 8. In nearly half the patients the FRC was 5 L. or more, and in nearly a fourth it was 6 L. or more. These are unusually large FRC values. They result from applying corrections to include the full amount of the slowest subdivision. In many cases these large subdivisions have so slow a gas exchange that even helium, which is highly diffusible, requires many minutes to wash out of them. The time required is often much longer than the conventional seven minutes

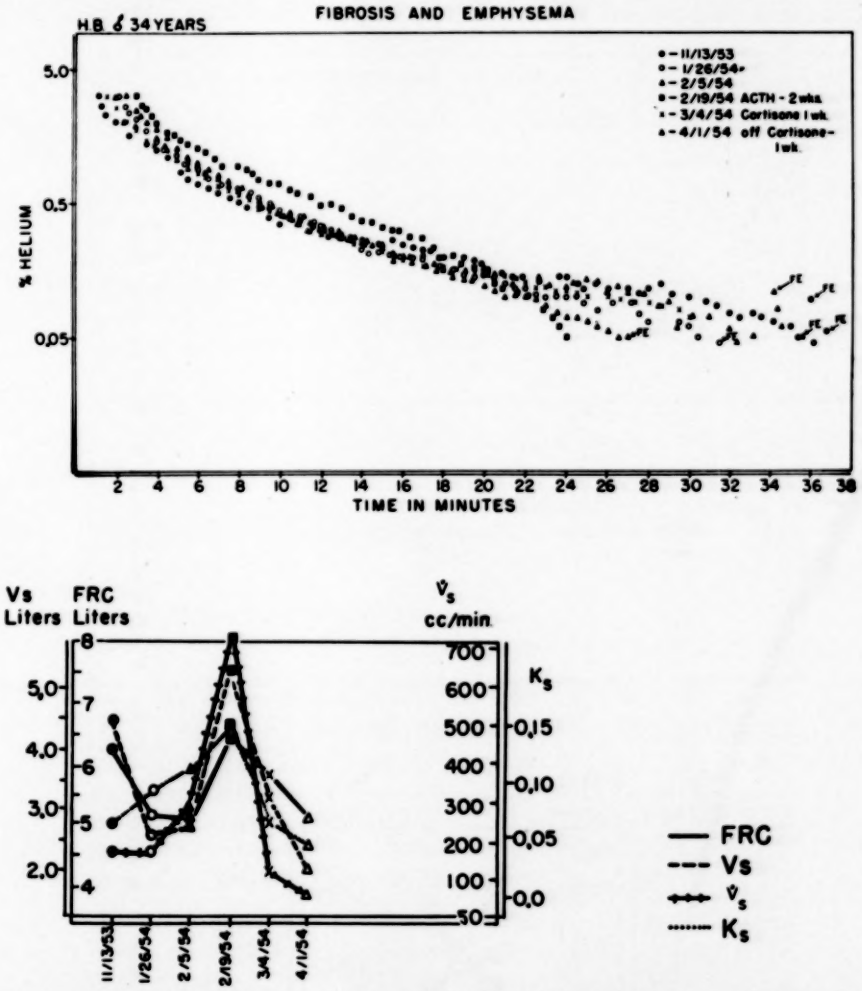

FIG. 5. Helium clearance curves of a patient with advanced pulmonary fibrosis and emphysema. The six studies extend over a period of four and a half months. There were changes in the size and ventilation rate of the most slowly ventilated space at the time of treatment with ACTH, but the slow space remains large and poorly ventilated during the entire period of study. "FE" denotes the maximum helium concentration reached as the result of a forced expiration at the end of the washout period.

which is often allowed as a washout or equilibration period for normal subjects in methods for measuring functional residual capacity. Consequently, the FRC calculated from the quantity of helium washed out of the lung in seven to ten minutes needs correction for the amount by which original filling of the slowest space with helium was incomplete, and for the amount by which the subsequent washout was incomplete. These corrections are deduced from the characteristics of the slow space. Table II illustrates how large the corrections may be by comparing in several subjects the FRC which would be calculated on the basis of a seven-minute washout with the FRC which resulted from prolonging the washout for periods up to forty-one

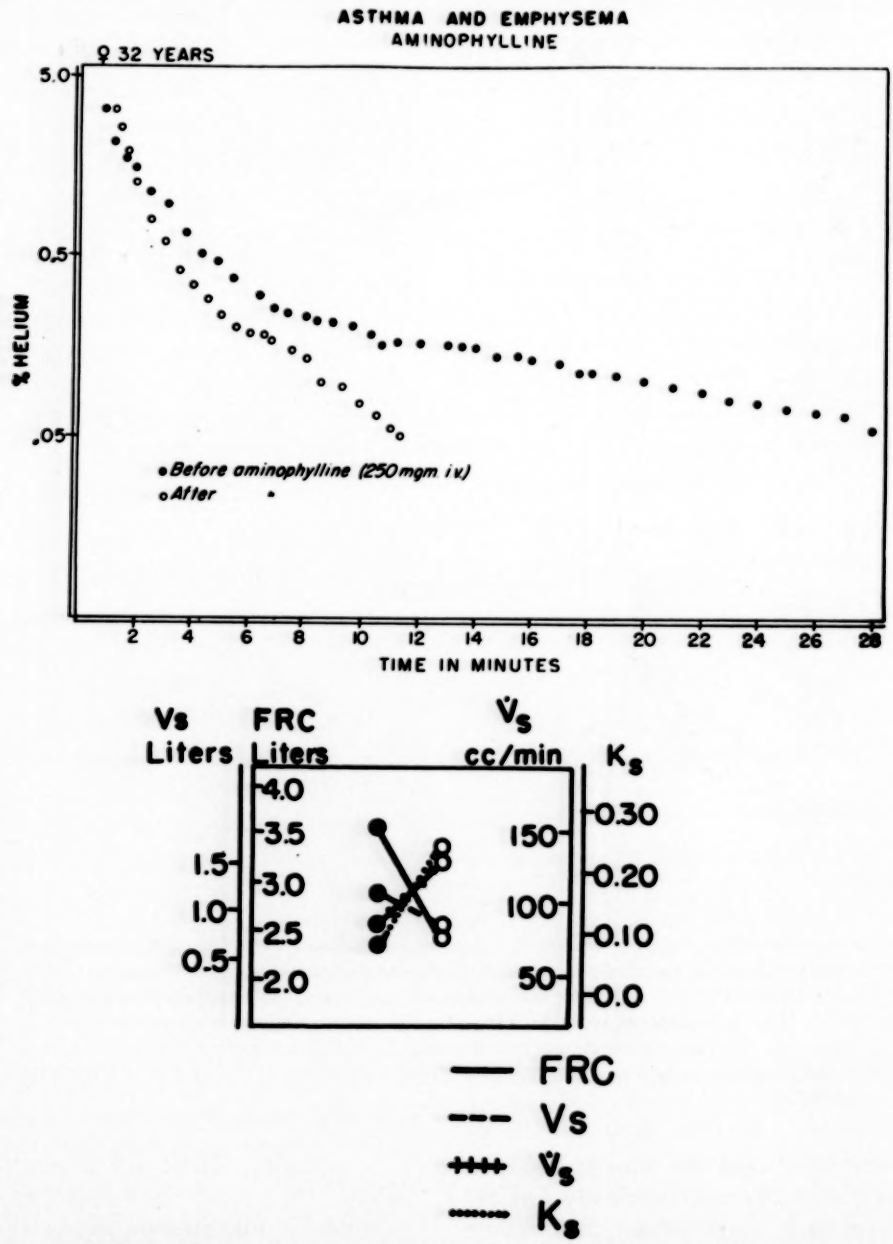

FIG. 6. Helium clearance curves of a thirty-two year old woman with asthma and emphysema before and after administration of aminophylline. The patient was not having a frank asthmatic attack at the time of the study. It is apparent from the clearance curves and from the accompanying diagram that aminophylline caused an increase in the ventilation rate and a decrease in the size of the "slow space." There was also a substantial decrease in the FRC.

minutes and with the FRC for which complete corrections have been made. Differences between the fully corrected value (FRC_c) and that based on prolonged washout (FRC_t) depend on an allowance for failure of the lung to fill completely with helium in the preliminary fifteen-minute equilibration period. In Cases 1, 2, 5 and 9 this difference was substantial, indicating that even fifteen minutes was insufficient for a satisfactory equilibration. In most cases seven minutes was quite inadequate. These results indicate that helium methods which rely on reaching substantial equilibration within seven to ten minutes may seriously underestimate the FRC in severe cases of emphysema. It has been pointed out before that patients with severe emphysema cannot, in general, deliver an alveolar sample which fairly represents the mean gas concentration in the lung during a washout procedure.[4] For this reason methods of measuring the FRC which depend on a short washout period and an alveolar sample may also underestimate the FRC in very severe emphysema. Accurate measurement of the FRC in these cases requires a method which can make adequate allowance for the extremely slow gas exchange of some of these large subdivisions.

Relation between MBC, RC/TC Ratio and Intrapulmonary Mixing in Emphysema. Decrease in the maximum breathing capacity and increase in the ratio of residual to total lung volume are typical of pulmonary emphysema.[6] As shown in Figure 9, there was a striking correlation between the decrease in MBC and the increase in RC/TC ratio among the subjects of this study. In general, clinical estimates of the severity of the disease agreed well with the degree of abnormality shown by these tests. It is apparent from Figure 9 that unusually large RC/TC ratios were found in many of these subjects. This is a result of the ability of the present method to uncover large FRC values, and consequently large residual capacities, in patients with advanced emphysema.

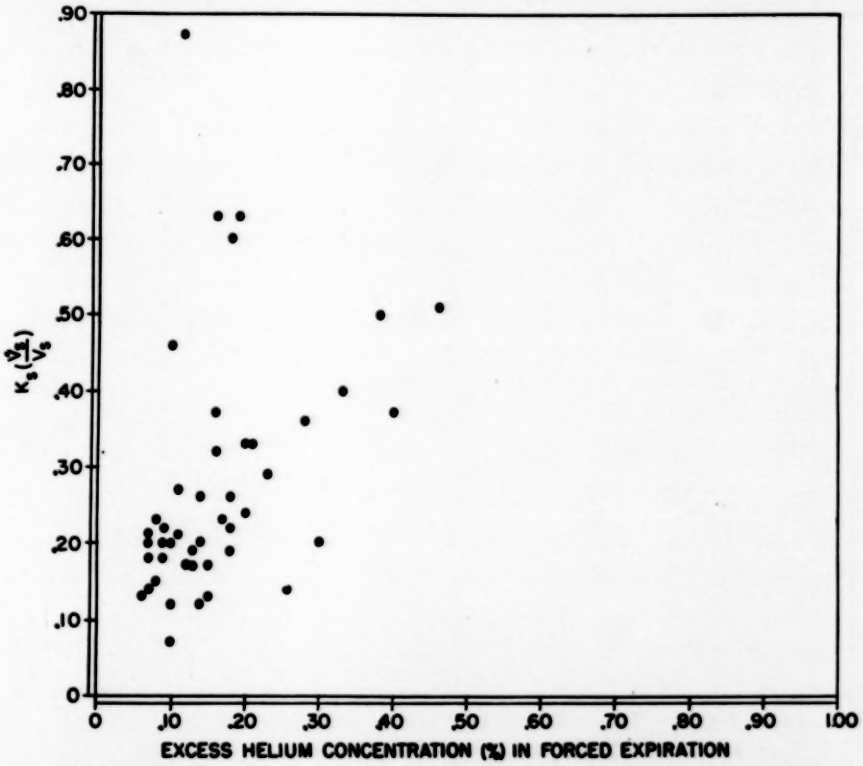

FIG. 7. The effect in emphysematous patients of a forced expiration after "washout" of the lungs has proceeded until the helium concentration of expired air has fallen to 0.05 per cent. The helium concentration is increased in the forcibly expelled air, and the highest concentration recorded by the katharometer is plotted on the abscissa of the figure. The k_s or ratio between minute ventilation rate and volume of the slow space is plotted on the ordinate. In general, the poorer the ventilation of the slow space, the less it is affected by a forced expiration.

Mixing defects occur regularly in emphysema. This is apparent from Figure 2. However, the defect in intrapulmonary mixing, as measured by the size of the slowest space, is not closely related to change in MBC or RC/TC ratio. In general, subjects with only minor changes in MBC or RC/TC ratio have relatively small slow spaces. A large slow space is unusual in such a subject. However, marked changes in MBC or RC/TC ratio may be associated with either a very large or a relatively small slow space. In these advanced cases the slow space whether large or small is usually very poorly ventilated.

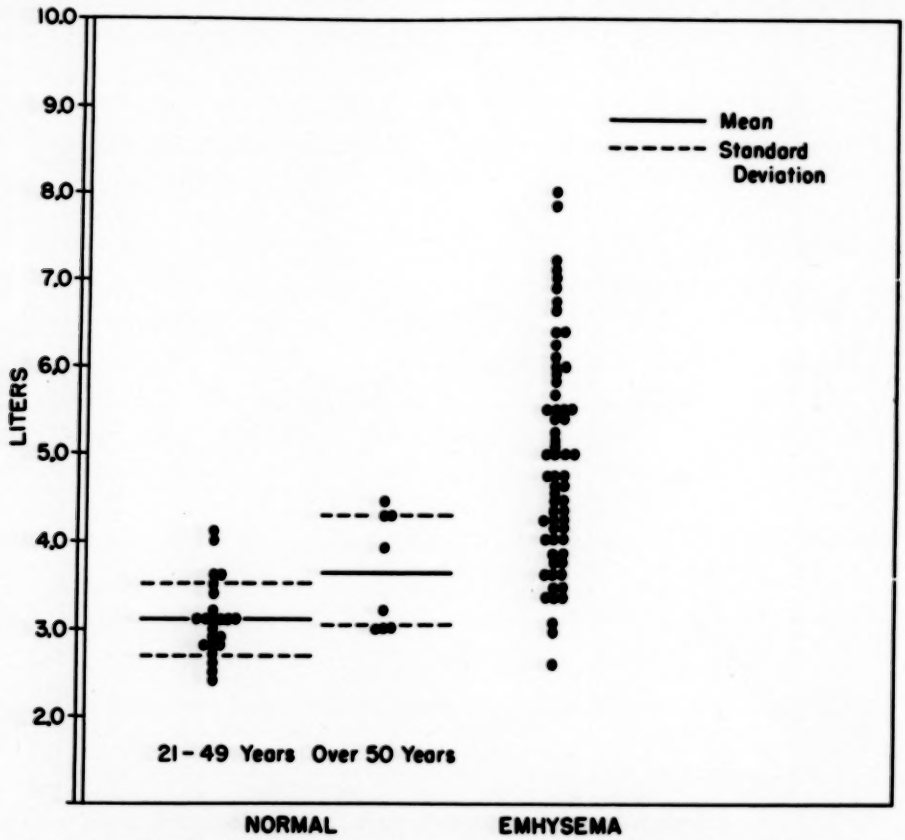

FIG. 8. Functional residual capacity of normal persons and patients with emphysema. Of the emphysematous patients, nearly half have an FRC over 5 L. and nearly a quarter have an FRC over 6 L.

COMMENT

The occurrence of slowly ventilated lung regions of considerable size in patients with emphysema has been described recently by other investigators.[1-3] The poorly ventilated spaces found in the present patients tend in general to be larger and to have a slower ventilation rate than those reported in previous studies. The detection and measurement of these spaces requires a sensitive analytical system. The use of such a system in the present study is responsible for uncovering the very slow large spaces and the unusually large functional residual capacity of many of these patients. Because of the large values obtained for functional residual capacity in the present patients with severe emphysema the estimated total lung volume in most cases is considerably larger than normal. In previous studies the total lung volume in severe emphysema has been found to be about normal in size.[6,7]

The anatomic distribution of these slowly ventilated spaces in patients with emphysema is not known. It was the belief of Tendeloo, supported by Roelsen,[8] that the peripheral portions of the lung, in which emphysema was most advanced, were the best ventilated portions and that the central regions, which were less affected by the disease, were most slowly ventilated. It appears more likely, however, that the regions where emphysematous changes are most severe would be the worst ventilated. It is apparent

that the slow spaces in emphysema are poorly perfused with blood as well as being poorly ventilated: otherwise cyanosis would be a consistent rather than an occasional clinical feature of severe emphysema. This evidence that both circulation and ventilation are much impaired in the slowly ventilated spaces suggests that these regions are the ones in which the disruptive changes of emphysema are most advanced.

There is relatively little information about the relation between perfusion and ventilation in the unevenly ventilated lungs of persons with emphysema. Although perfusion is reduced far below normal in the poorly ventilated regions, it appears to be maintained proportionately somewhat better than ventilation, as indicated by the low RQ in air driven from these regions by a forced expiration.[9,10] In severe emphysema some portions of the lung must be grossly overventilated, as pointed out by Briscoe.[3] This is also evident from inspection of Table 1. If the values for ventilation rate and volume of the slowly ventilated regions are subtracted from the total minute ventilation rate and the functional residual capacity, it is apparent in many cases that the average ventilation rate for the remainder of the lung is abnormally high. The excess ventilation must be directed into regions with a low perfusion rate; otherwise the arterial carbon dioxide tension would be normal or reduced, rather than elevated in advanced emphysema. In emphysema it appears that neither the grossly overventilated nor underventilated portions of the lung are well perfused with blood.

The existence of large, slowly ventilated, slowly perfused lung spaces in patients with emphysema appears to account for the prolonged after-effect of breathing oxygen which some of these persons demonstrate. When oxygen is administered for twenty to thirty minutes to an emphysematous person who exhibits definite arterial oxygen unsaturation

TABLE II
COMPARISON OF VALUES OF CALCULATED AND CORRECTED VOLUMES OF THE FRC*

No.	Patient	FRC_7[1]	FRC_t	Total Collection Time (min.)	FRC_c	V_s	K_s
1.	W. W.	3.77	5.59	41.0	6.69	4.75	.10
2.	A. T.	4.10	4.90	26.2	5.49	2.78	.13
3.	W. S.	4.52	4.74	16.8	4.74	1.00	.18
4.	B. S.	4.56	5.16	17.0	5.48	1.91	.15
5.	H. B.	3.44	4.07	32.0	5.16	2.56	.09
		3.65	4.37	26.5	5.07	2.74	.12
		4.37	5.09	24.0	6.52	5.30	.15
		3.31	4.39	30.0	5.83	3.22	.06
		3.12	4.43	30.0	5.07	2.00	.04
6.	J. A.	4.54	5.81	20.3	6.21	2.56	.12
7.	L. S.	5.35	6.12	18.5	6.33	3.65	.20
8.	R. K.	7.00	7.78	19.0	7.83	5.42	.23
		6.72	8.09	22.0	8.25	5.54	.21
		5.94	7.31	20.0	7.23	4.95	.21
		6.76	8.26	23.4	8.24	4.48	.19
		6.02	7.93	30.0	7.91	6.50	.17
9.	C. H.	5.07	6.97	32.0	8.47	7.24	.15
10.	J. B.	5.07	5.18	18.0	5.27	.85	.17
11.	C. L.	3.64	3.87	16.3	3.97	1.10	.20

FRC_7[1]—FRC calculated from seven-minute expired air collection.
FRC_t—FRC calculated from prolonged collection.
FRC_c—Corrected FRC.
V_s—Volume of slow space.
K_s—Flow/volume of slow space.
* All volumes are expressed in L. @ BTPS.
The difference between FRC_t and FRC_7 ($FRC_t - FRC_7$) results from continued excretion of helium after the initial seven minutes of washout time. The large differences which may occur illustrate the need for allowing long periods for washout in patients with severe impairment of intrapulmonary mixing. The difference between FRC_c and FRC_t ($FRC_c - FRC_t$) is the correction required for failure of the lungs to fill adequately with helium during the preliminary fifteen-minute equilibration period.

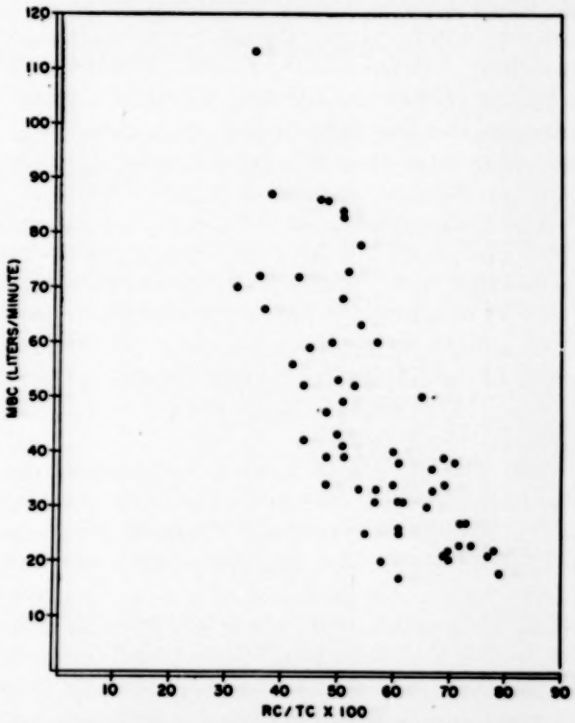

FIG. 9. Relation between maximum breathing capacity and ratio of residual to total lung volume in patients with pulmonary emphysema.

while breathing air, the arterial unsaturation often returns only very slowly after the oxygen is discontinued. In some cases it may be well over twenty minutes before the oxygen saturation returns to the previous level.[11] The present results suggest that this phenomenon depends on filling a large, slowly ventilated space with oxygen which then, during subsequent air breathing, slowly washes out. During this washout period the oxygen which is released enriches the gas mixture in other portions of the lung and this delays the return to the previous level of arterial oxygen unsaturation.

The characteristics of the slow space appear to be fairly stable in advanced emphysema. The slow space can, however, be quite variable, both as to size and ventilation rate in persons with asthma, bronchitis or other reversible disorder of the respiratory system. In such persons it seems likely that the slow space may have no fixed anatomic location.

The present results have a bearing on the treatment of lung disease by aerosols. Asthma or bronchitis will intensify inequality of gas mixing in the lungs. Ordinary breathing will carry the aerosol to the most normal portions of the lung rather than where it is most needed. More vigorous breathing, including forced expiration as well as deep inspiration, will help to reach the poorly ventilated portions of the lung. In some cases prolonged administration will be required to deposit an adequate quantity of aerosol in a very slowly ventilated space. In some cases it will be impossible to reach diseased regions of the lung with an aerosol in adequate quantities.

SUMMARY AND CONCLUSIONS

1. By a sensitive open-circuit method using helium as the test gas, observations have been made on intrapulmonary gas mixing in sixty-one patients with pulmonary emphysema. Impaired mixing has been measured in terms of the size and ventilation rate of the "slow space." This is the sum of those lung regions which behave collectively as though they were a single space, homogeneously ventilated at the slowest rate of any space in the lung. In addition the conventional lung volumes, ratio of residual to total lung volume, and maximum breathing capacity have been measured.

2. Defective mixing occurs regularly in emphysema. There is wide variation but it is not unusual to find that half or more of the resting lung volume has a tenth or less of the normal over-all ventilation rate. In severe emphysema these slow spaces maintain the same general size and ventilation rate over a period of weeks or months. Ventilation of the slow space can be increased moderately by forced expiration but in severe emphysema the slow space does not contribute to a forced expiration in proportion to its volume.

3. The present method yielded unusually large values for the functional residual capacity. In about half the patients the FRC was over 5 L. and in about a fourth it was over 6 L.

4. The extent of abnormality in the MBC agreed well with the extent of abnormality in the RC/TC ratio. The severity of the disease as judged clinically was also in fair agreement with the severity as indicated by these tests. However, the defect in intrapulmonary mixing as measured by the size of the most slowly ventilated space, was not closely related to change in MBC or RC/TC ratio.

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Improved Apparatus for Determining the Functional Residual Capacity of the Lung by the Open Circuit Method*

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THE development of a pulmonary function laboratory soon progresses from the simple spirographic studies of lung volume to the addition of the more complex determination of functional residual capacity. We wish to describe a modified form of the open circuit method for determining the functional residual capacity which was elaborated during the evolution of our laboratory.

The functional residual capacity is the key to the derivation of the residual volume and hence the total lung capacity. All the other lung partitions may be determined directly from the spirogram. The functional residual capacity is the volume of gas remaining in the lungs at the end of a natural expiration. The value for this compartment must be obtained indirectly. The residual volume, which is the volume of gas remaining in the lung at the end of a maximum expiration, can be derived by simply subtracting the spirographically determined expiratory reserve volume from the functional residual capacity. The total lung capacity is the sum of the vital capacity and the residual volume. The ratio of the residual volume to the total lung capacity × 100 is frequently used as an index of the degree of hyperinflation of the lung. Normal values are considered to be less than 35 per cent although Greifenstein[1] and others have shown that the value increases somewhat with age.

Certain pathologic conditions are accompanied by alteration in the functional residual capacity and the residual volume. An increase in these values occurs with hyperinflation of the lung or the development of emphysema. Our laboratory is engaged in a long-term study of hyperinflation of the remaining overexpanded lung following segmental resection or lobectomy, which is performed in over 50 per cent of our tuberculosis patients to remove residual disease. The question remains unanswered whether or not overexpansion of lung tissue may eventually lead to emphysema and yet this may be an important consideration in the future welfare of our patients. Residual volume studies are helpful also in evaluating advanced emphysematous patients as surgical risks. Determinations are made on non-surgical cases in routine investigation and in the evaluation of therapy of patients with pulmonary diseases such as asthma, chronic bronchitis, emphysema, cystic lung disease and pulmonary fibrosis.

METHOD

A number of indirect methods have been described for measuring the functional residual capacity. The most widely used are the Christie closed method,[2] the helium method,[3,4] analysis of pulmonary N_2 clearance using a nitrogen meter by the method of Fowler[5] and the Darling method.[6] The simplicity and accuracy of the last are desirable features. The component parts of the apparatus are available in most pulmonary function laboratories. The original method described by Darling used a Tissot apparatus for collecting the expired air. This method was found to be cumbersome and involves a large dead space. Due to the small excursion registered with each breath into the Tissot apparatus, difficulty was encountered in determining whether the patient had been connected with the O_2 circuit exactly at the end of the expiration. The modification of Gaensler using a respirometer has proved satisfactory. This

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allows the patient to breathe room air until the ventilation becomes regular and the change to the O_2 circuit can be made at the end of an expiration with facility. In our laboratory a balloon circuit of the Collins bronchospirometry assembly is used for this purpose. During the seven-minute test while the patient is breathing O_2, the expired air is collected in a Douglas bag or meteorologic balloon and later measured in a Tissot apparatus. The alveolar sample at the end of seven minutes of oxygen breathing is obtained from a Haldane alveolar sampling apparatus, with the expired air passing out through a water trap. By watching the decreasing number of bubbles one can readily judge the time at which to draw the sample to best advantage, and a valve can be turned to prevent sucking back the water with the next inspiration. A small water trap is connected with the side arm of the sampling chamber through which the air is cleared as well. The whole system of valves, tubing, mouth piece and the Haldane alveolar sampling device are mounted on plywood which is attached to an over-the-bed table in place of the top. This allows easy adjustment of the mouth piece to the patient's level with a short piece of tubing between the mouth piece and the four-way valve, thus reducing the dead space to a minimum.

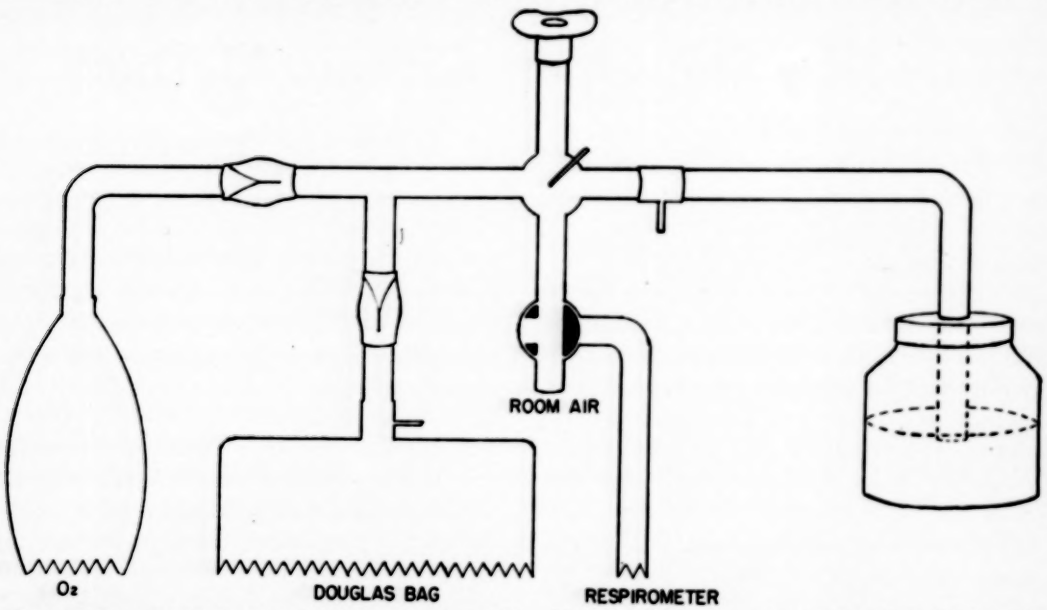

FIG. 1. Diagram of circuits for determination of functional residual capacity and index of intrapulmonary mixing.

Figure 1 shows the circuits which are used. The following equipment is required: Large oxygen tank containing 99.4 per cent O_2 and reduction valve, a small tank of O_2, a 13-L. anesthesia bag, bronchospirometry assembly or respirometer, two flutter valves, four-way valve, mouth piece, nose clip, a small water bottle with tubing, a pint jar with screw top, 1 inch rubber tubing, sampling couple, Douglas bag 60 L. or large meteorologic balloon, stop watch, four sampling chambers and a Scholander apparatus for micromethod of gas analysis.

Figure 2 is a photograph of the apparatus in use.

The patient is brought to the laboratory in the resting state and without breakfast. He is placed in the hospital bed sitting at an angle of 45 degrees and made as comfortable as possible. The test is explained to the patient and he is taught how to exhale correctly. While he is resting a few minutes, the circuit and bag or balloon are washed out three times with O_2 and the anesthesia bag is left three-fourths full and hung well below the level of the patient. The patient is then connected with the circuit of the spirometer. The respiratory excursions are carefully watched; and when the base line becomes even and no leak is demonstrated, he is switched into the O_2 circuit exactly at the end of expiration. The flow of O_2 from the tank into the anesthesia bag is adjusted to supply his requirements. During the last two minutes of the seven-minute run the Haldane alveolar sampling device is flushed out with O_2 from a

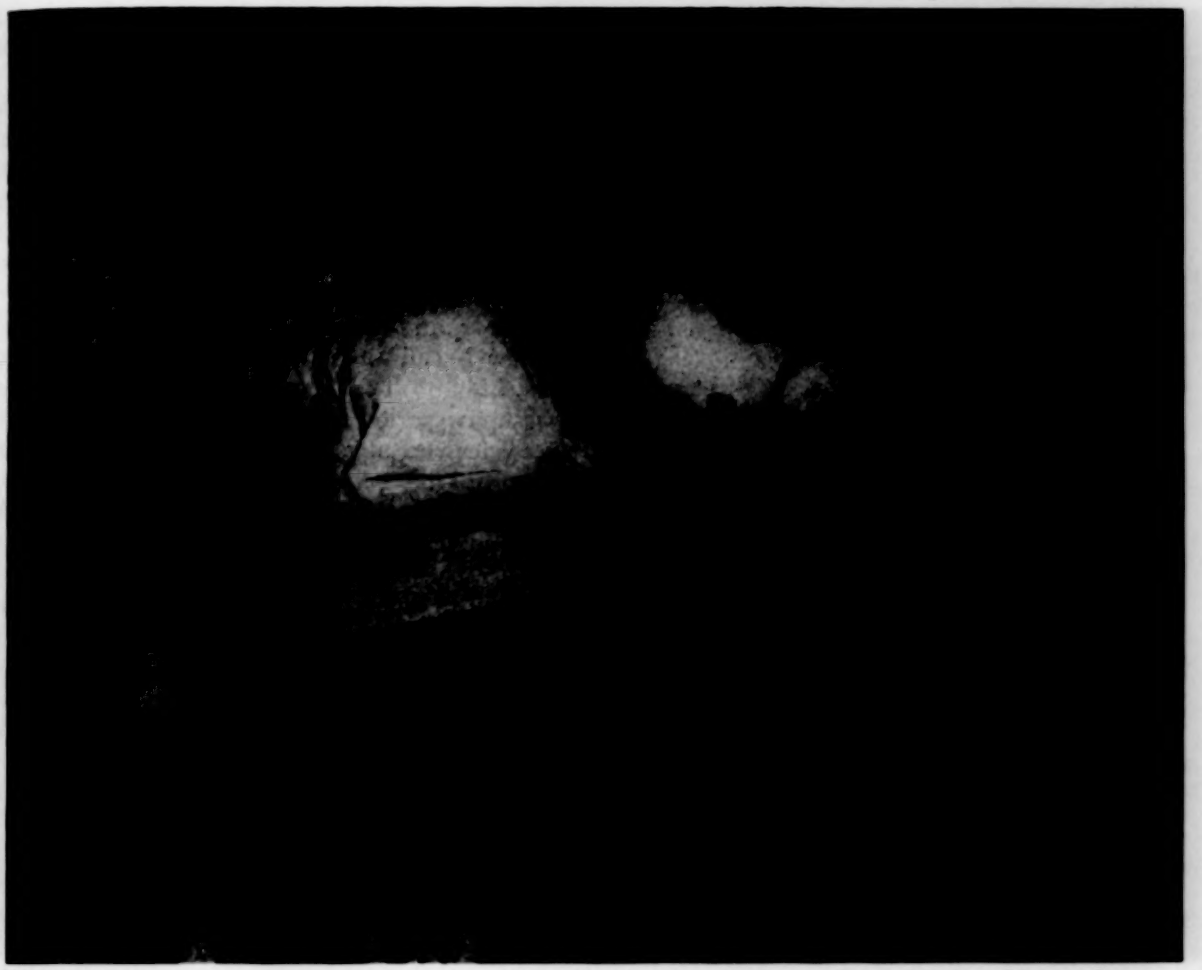

FIG. 2. Photograph of apparatus used for determining functional residual capacity and index of intrapulmonary mixing.

small tank and the opening in the tube is adjusted in the water trap to come just below the surface. The patient is alerted fifteen seconds before the end of the test and at seven minutes is asked to expire as much air as possible from his lungs. The sample is collected while the last bit of air is being expelled. The tubing to the bag is washed with several hundred cc. of O_2 and then the gas in the bag is thoroughly mixed and a sample obtained. The bag is then clamped off and attached to the Tissot apparatus for evacuation and measurement of the total volume expired in the seven-minute period. Duplicate samples are run on the Scholander for N_2 content.

The formula

$$\text{FRC (dry)} = \frac{(V + DS)(NS - NO) - C}{81 - \text{Alv. N}}$$

is used in the calculation, as described by Darling.[5] After forty-five minutes the test is repeated and the results should closely approximate the first run.

RESULTS

Table 1 shows the results obtained by this method on duplicate samples of seventy-one consecutive patients.

TABLE 1

RESULTS OF SEVENTY-ONE DUPLICATE FUNCTIONAL RESIDUAL CAPACITY DETERMINATIONS BY THE OPEN CIRCUIT METHOD

	Deviations from the Mean of the Paired Values (%)				
	Less than 2	2-3	3-5	5-7	More than 7
Number of patients	35	12	14	5	5
Percentage of patients	49	17	20	7	7
Mean values for FRC (cc.)	3,100	3,515	3,085	3,204	2,556

It is seen that in thirty-five duplicate tests 49 per cent of the whole series deviated less than 2 per cent from the mean of the pair of values. In forty-seven duplicate tests, or 66 per cent, the deviation was less than 3 per cent. In sixty-one duplicate tests, or 86 per cent, the deviation was less than 5 per cent, and in sixty-six cases, or 93 per cent, the deviation was less than 7 per cent. There is no apparent correlation between these deviations and the size of the functional residual capacity.

COMMENT

This apparatus has been monitored for accuracy and leaks in the following manner. The described test might be subject to error because no spirogram is taken during the seven-minute washout period. A leak might develop which will not be recognized. Hyperventilation might occur, with attendant inaccuracy. Furthermore, a shift in the base line might take place which will in turn change the FRC. To check these possibilities an apparatus was constructed according to the suggestion of Dr. Ward A. Fowler in which two meteorologic balloons of 150 L. capacity are contained in a 55 gallon oil drum which is made air-tight.[7] The top was cut out of this drum and fitted with a thick plastic top securely pulled down by 12 bolts against a rubber gasket and finally sealed with paraffin. Through the plastic top at appropriate places three holes of 3 inch diameter were bored which allowed insertion of the two balloons on number 10 stoppers bored to take the connecting tubing. One balloon receives the O_2 for the test, approximately 70 to 100 L. The other balloon collects the expired air during the test. The third opening receives the connection to the spirometer which makes the graphic record during the test. A thermometer was also inserted in this stopper. A constant temperature was found necessary to obtain a tracing with a straight horizontal base line. O_2 saturated with water vapor is also used to obviate the change from dry to wet gas during this test. At the end of the test after the tubing has been cleared by a few hundred cc. of O_2, the stopper to the respirometer circuit is removed and a stick inserted into the barrel to mix the gases in the collecting balloon. This balloon system was found to work very efficiently and did not significantly change the results obtained in control and diseased subjects. Furthermore, we have not found any patients who hyperventilated or varied their base line significantly.

We have further monitored the apparatus by the use of a Waters-Conley nitrogen meter which has recently become available in our laboratory. The No. 26 hypo-sampling needle is placed in the mouth piece and the needle held securely by a plastic holder devised in our laboratory. It is connected to the nitrogen meter by an 8 inch piece of tubing. The nitrogen meter is calibrated and operated as described by Lilly.[8,9] The record of the seven-minute washout period is obtained on a Sanborn recorder run at a slow speed. Near the end of the run the gain is increased to allow more sweep of the stylus to obtain the alveolar sample N_2 and this is followed by a calibrated sample of 7.5 per cent N_2. This method allows one quickly to detect any leaks of room air into the system around the mouth piece. None were found to occur during the seven-minute washout period. Care must be taken to instruct the patient during the forced expiration to keep his lips tightly around the mouth piece as some leakage of air may occur during the effort to expire all the air out of the lungs.

The nitrogen meter is helpful in giving a visual picture of the washout of N_2 during the seven minutes of O_2 breathing. The curve drops sharply toward the zero line in normal controls and takes a longer time in the emphysematous patients. The rate of clearance is a function of the effective alveolar ventilation as shown by Fowler, Cornish, and Kety.[5] Our studies show that in the normal patient a total ventilation of less than 20 L. will bring the expired N_2 level to below 7.5 per cent. For patients with poor mixing and emphysema a large ventilatory volume is necessary to wash out N_2 to this critical level on the curve.

The curve obtained with the N_2 meter at the end of the seven-minute washout gives an accurate reading of the alveolar N_2 when the patient carries out a maximum expiratory effort. Alveolar samples taken by the Haldane method are generally inaccurate and strict duplication of two successive tests is rarely obtained in abnormal patients. This is due in part to the fact that samples are not taken at the same point in expiration from the Haldane sampler. The graphic record obtained by the N_2 meter in the N_2 washout procedure is therefore most useful in monitoring the open

circuit method and gives valuable additional information.

DISCUSSION

The functional residual capacity determinations made by the open circuit apparatus described show satisfactory agreement between duplicate samples. As others have observed, the greater the FRC the less accurate becomes the determination of the index of intrapulmonary mixing. Fifty-four per cent of our patients tested had $\frac{RA}{TC} \times 100$ values over 35 per cent and all but seven of this group had elevated indices of intrapulmonary mixing. Eight patients with normal $\frac{RA}{TC} \times 100$ values had abnormal indices of intrapulmonary mixing (greater than 2.5 per cent). These patients all had cavitary disease or localized emphysematous blebs. Twelve patients with residual air studies indicating emphysema underwent pulmonary resection and all but three were demonstrated at operation or by pathologic sections to have emphysema. It should be emphasized that the open circuit method will detect the changes of emphysema only if moderately advanced or severe. Studies are now being carried out at this laboratory to perfect a satisfactory method to detect emphysema in an early stage of development.

SUMMARY

A modification of the open circuit method is described for determination of the functional residual capacity and index of intrapulmonary mixing. The method is simple, inexpensive and sufficiently accurate for routine use.

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Effects of the Carbonic Anhydrase Inhibitor "6063" (Diamox) on Respiration and Electrolyte Metabolism of Patients with Respiratory Acidosis*

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It is well known that the oral administration of "6063" (diamox®)‡ will regularly produce an increase in urinary excretion of bicarbonate, sodium, potassium and water which results in a decreased plasma bicarbonate and the development of hyperchloremic acidosis. These effects of diamox are thought to be mediated by interference with the normal acidifying mechanisms of the kidney through inhibition of renal carbonic anhydrase activity.[1] Nadell[2] has observed that the fall in plasma bicarbonate and pH induced by administration of diamox to patients with respiratory acidosis was followed subsequently by clinical improvement and by a decrease in PCO_2. Since the PCO_2 level is under pulmonary control, the fall in arterial PCO_2 was attributed to respiratory compensation for the diamox-induced metabolic acidosis, i.e., hyperventilation, although respiratory variables were not measured in these studies. Galdston et al.[3,4] reported that in normal patients the decreased plasma bicarbonate induced by diamox is accompanied by concurrent hyperventilation and decrease in PCO_2, this latter effect tending to minimize the fall in blood pH. However, these authors were unable to demonstrate a similar consistent reduction in PCO_2 in patients with advanced pulmonary emphysema. Thus reduction in PCO_2, a desirable therapeutic effect for patients with respiratory acidosis, appears to be an inconstant effect of the administration of diamox to these patients.

The present study was undertaken to observe the effects of diamox on ventilation and other respiratory variables, as well as on PCO_2, and to extend observations on electrolyte metabolism and the clinical response of patients with chronic respiratory acidosis secondary to chronic pulmonary emphysema.

MATERIALS AND METHODS

Eleven studies were performed in seven patients with CO_2 retention secondary to chronic pulmonary emphysema. Repeated pulmonary function studies in five cases over a period of two to four years, and in the two other cases for a period of five months, confirmed the diagnosis of pulmonary emphysema and chronic CO_2 retention. Six of the seven patients had severe but uncomplicated pulmonary insufficiency with arterial oxygen saturation below 92 per cent and a carbon dioxide tension above 48 mm. Hg following a standard exercise test.[5] At the time of the study there was no evidence of cardiac decompensation in any of the patients. Six were free from acute infections at the time of the study and gave no evidence of renal insufficiency. One patient (G. Z.) was admitted to the hospital in acute pulmonary decompensation secondary to an acute respiratory infection and was in clinical shock with oliguria at the time diamox was given. All patients were in the hospital at the time the initial dose of diamox was given and remained for at least two weeks during daily administration of the drug.

‡ 2-acetylamino-1,3,4-thiadiazole-5 sulfonamide.

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Throughout their hospitalization the dietary intake of sodium was restricted to approximately 2 gm. per day.

The effects of continued oral administration of diamox for from eighteen to fifty-four days were observed in six patients. At stated intervals twenty-four-hour urine specimens were collected under mineral oil with a small amount of thymol added in the collection bottle kept on ice at the patient's bedside. The urine volume, pH, CO_2[6] and chloride[7] of these twenty-four-hour specimens were measured. The pH was determined at approximately 25°C. utilizing the Cambridge research model pH meter. Urine sodium and potassium were determined by the internal standard flame photometer.

All patients were thoroughly familiar with the procedures employed for collection of expired air and arterial blood, were in the postabsorptive state, and were given an ample rest period after the arterial needle was in place and before the study was started. Through an indwelling needle in a brachial artery, samples of arterial blood were collected anaerobically in a syringe containing a heparin-sodium fluoride solution and a drop of mercury for agitation. Sodium fluoride and mercury were omitted from samples collected for determination of electrolytes. Whole blood was analyzed for pH, CO_2 content,[6] and PCO_2 and PO_2 by the direct method of Riley.[8] The pH of whole blood was determined at 37.5°C., utilizing a Cambridge pH meter with a constant temperature water-jacketed glass electrode. Whole blood CO_2 content was converted to serum CO_2 utilizing the line chart of Van Slyke and Sendroy.[9] The PCO_2 was then calculated from the serum CO_2 and the whole blood pH, utilizing the Henderson-Hasselbalch equation and a pK value of 6.1 for H_2CO_3. The PCO_2 so calculated served as a check on the directly determined PCO_2 and regularly checked the PCO_2 determined by the direct method within 3 mm. Hg.

Inspired air was supplied by a compressed air tank and expired air was collected in a Tissot spirometer. After a ten-minute washout period a three-minute spirographic tracing of ventilation was recorded. A five-minute collection of expired air was then made, with arterial blood samples drawn in the middle one and a half minutes of gas collection. Total minute ventilation was taken as the average minute volume during the five-minute collection period. Inspired and expired air were analyzed for O_2 and CO_2 content using the micro-Scholander gas apparatus.[10]

The acute effects of a large oral dose of 25 mg. per kg. body weight of diamox were studied in five patients. An indwelling catheter was inserted and two one-half-hour control urines were collected under mineral oil; after administration of diamox, one-, two-, three- and four-hour specimens were collected in a like manner. Two control arterial blood and expired air samples were collected one hour before and immediately before administration of diamox, additional samples being collected at one-, two-, three- and four-hour intervals after administration of the drug. Urine, arterial blood and expired air were analyzed in the same manner as in the studies on protracted use of diamox.

RESULTS

Chronic Changes. The effects of continued oral administration of diamox (10 mg. per kg. body weight per day in four divided doses) were studied in six patients. (Tables I and II.) In all four patients in whom urinary constituents were measured, carbon dioxide excretion increased fourteen- to eightyfold and urine pH increased 1.0 to 2.5 pH units in the first twenty-four-hour urine collection after administration of diamox. During this twenty-four-hour period chloride excretion was reduced in all except one case (S. B.), in which chloride excretion was found to have doubled. This patient also had a vigorous diuresis of 5,600 cc. during the first twenty-four hours. In the two cases studied, sodium and potassium excretion was increased significantly. Urine pH, CO_2 and electrolyte excretion returned to control values within three days in all but one patient (F. M.), and in this case urinary pH, CO_2 and potassium excretion remained above control levels during twenty days on the drug. As judged by twenty-four-hour urine volumes and body weight, a significant diuresis occurred consistently during the first twenty-hour hours of drug administration but was not sustained after the third day of diamox dosage.

Plasma chloride levels rose by the third or fourth day of therapy, as the plasma bicarbonate levels fell. No consistent changes in plasma sodium or potassium levels occurred. Throughout the period of drug administration plasma bicarbonate was depressed below control values, the maximum depression (ranging from 3.3 to

9.2 mEq./L.) usually occurring on the third or fourth day of drug administration. At that time the arterial blood pH was likewise maximally reduced from 0.03 to 0.15 pH units below control values. After reaching lowest values on the third or fourth day, plasma bicarbonate and pH levels gradually returned toward, but never reached, control values as long as the drug was continued. Arterial PCO_2 was reduced significantly in all cases, the maximum depression being reached in from three to sixteen days. Since the pH remained below control (and normal values) throughout the period of drug administration, plasma bicarbonate reduction was disproportionately larger than reduction in PCO_2.

Arterial PO_2 increased significantly within three to four days in all cases, attaining levels 14 to 20 mm. Hg. in excess of control levels after a week or more on the drug.

TABLE 1

EFFECTS OF CONTINUED ORAL ADMINISTRATION OF DIAMOX (10 MG./KG.) ON URINARY EXCRETION IN FOUR PATIENTS WITH RESPIRATORY ACIDOSIS

Patient	Day	Weight (kg.)	Volume (24 hr.)	pH	CO_2 (mEq./24 hr.)	Cl (mEq./24 hr.)	Na (mEq./24 hr.)	K (mEq./24 hr.)
J. H.	−2	104.2	....	....	.....	.....	....	....
BSA * 2.22	−1	104.0	380	5.59	1.2	20.9	....	....
	1	103.2	1050	7.31	73.6	11.3	.....	....
	2	101.4	880	6.93	15.3	13.4	....	....
	3	101.5	....	....	.....	.....	....	....
	4	101.5	725	6.54	4.6	.....	....	....
	7	100.4	1340	6.40	1.1	.....	....	....
	13	100.6	....	....	.....	.....	....	....
	33	101.0	....	....	.....	.....	....	....
S. B. †	−1	62.8	2040	6.59	8.0	73.4	....	....
BSA 1.79	1	59.1	5263	7.80	206.0	180.0	....	....
	3	58.2	2500	6.73	16.0	84.2	....	....
	6	59.1	1830	6.72	14.9	47.8	....	....
	10	57.8	1210	6.41	4.2	51.6	....	....
	16	58.0	....	....	.....	.....	....	....
	23	58.2	....	....	.....	.....	....	....
	44	58.1	....	....	.....	.....	....	....
F. B.	−1	58.2	810	6.53	4.9	33.5	38.5	31.5
BSA 1.68	1	57.8	1604	7.51	70.0	4.6	45.6	68.2
	2	56.8	880	7.07	10.9	6.8	12.2	33.3
	3	57.2	950	6.66	7.9	9.4	11.9	38.5
	4	.....	655	6.61	3.0	7.6	8.1	20.9
	5	.....	1170	6.47	3.8	9.2	8.9	36.7
	6	57.1	1160	6.57	6.7	2.2	13.5	42.5
	10	56.9	1230	6.67	9.5	34.8	39.5	39.0
	35	54.2	780	6.07	.....	18.6	7.4	20.2
	49	54.4	935	6.96	9.9	27.0	22.6	22.4
F. M.	−2	46.2	950	5.75	0.77	77.1	77.1	22.5
BSA 1.52	−1	.....	1350	4.93	0.84	69.0	41.1	29.5
	1	.....	1356	7.43	72.7	34.3	92.0	54.4
	2	.....	925	7.23	23.4	41.2	71.6	42.8
	3	.....	950	6.52	8.3	73.5	68.6	50.0
	4	44.4	956	5.92	1.9	79.7	50.0	60.5
	7	44.4	1480	6.40	8.5	93.7	77.8	55.0
	11	44.7	1200	6.41	5.6	67.7	67.8	25.5
	18	44.8	1195	5.81	2.5	111.0	94.6	35.5

* BSA = body surface area.

† Received 25 mg./kg./day for 9 days.

Initially, oxygen consumption and CO_2 output were slightly elevated in three of the four patients studied in this connection. A reduction of oxygen consumption and CO_2 output without significant change in respiratory quotient in the first week on diamox was found in these three patients. The ventilatory response to administration of diamox was not consistent and the change of small and probably not significant magnitude. In three patients an average increase of from 0.5 to 1.3 L. per minute occurred, while in a fourth case minute ventilation decreased an average of 0.5 L. In spite of these inconsistencies in total ventilation, alveolar ventilation, as

TABLE II

EFFECTS OF CONTINUED ORAL ADMINISTRATION OF DIAMOX (10 MG./KG./DAY) ON RESPIRATORY GASES AND ARTERIAL BLOOD IN SIX PATIENTS WITH RESPIRATORY ACIDOSIS

Patient	Day	Ventilation				Arterial Blood							
		Ventilation L./min./M² BTPS	O_2 Consumption (cc./min.)	CO_2 Output (cc./min.)	R.Q.	pH	$EHCO_3$ (Plasma) (mEq./L.)	PCO_2 (mm. Hg)	PO_2 (mm. Hg)	O_2 Saturation (%)	Cl (mEq./L.)	Na (mEq./L.)	K (mEq./L.)
J. H.	−2	....	.....	.....	....	7.39	35.9	61	...	....	.....	.....	...
BSA 2.22	−1	4.58	306.0	244.0	0.80	7.34	30.9	59	55	85.8	98.7	147.6	4.8
	3	5.65	313.1	255.1	0.81	7.31	23.6	45	68	93.6	103.0	154.0	3.8
	7	5.78	314.4	242.3	0.77	7.29	24.6	49	76	92.8	107.1	132.0	4.7
	13	6.32	345.3	277.3	0.80	7.32	22.5	45	76	92.2	.....	.....	...
	33	5.74	318.4	247.4	0.78	7.26	24.2	52	69	90.9	110.2	142.1	3.7
E. B.	−21	....	.....	.....	....	7.40	32.0	53	79	94.0	.....	.....	...
BSA 1.46	−1	....	.....	.....	....	7.37	31.9	57	71	92.1	.....	.....	...
	4	....	.....	.....	....	7.29	23.6	50	103	97.1	.....	.....	...
	9	....	.....	.....	....	7.33	21.9	43	93	95.0	.....	.....	...
	11	....	.....	.....	....	7.29	24.8	53	84	92.3	.....	.....	...
	15	....	.....	.....	....	7.32	25.5	51	80	91.5	.....	.....	...
	21	....	.....	.....	....	7.29	26.3	56	80	91.2	.....	.....	....
	29	....	.....	.....	....	7.28	25.6	56	101	98.8	.....	.....	...
	35	....	.....	.....	....	7.30	26.1	55	81	93.3	.....	.....	...
	43	....	.....	.....	....	7.26	24.4	56	81	91.9	.....	.....	...
	53	....	.....	.....	....	7.29	26.1	56	69	87.6	.....	.....	...
S. B.*	−20	....	.....	.....	....	7.42	33.9	54	43	77.2	.....	.....	...
BSA 1.79	−1	4.84	239.0	196.4	0.82	7.40	31.9	53	43	79.3	104.4	137.1	4.4
	3	5.28	238.0	192.5	0.81	7.27	22.7	51	51	80.2	111.1	143.3	4.2
	6	4.76	211.0	169.6	0.80	7.25	23.3	55	52	86.6	.....	.....	...
	8	5.61	212.0	205.2	0.97	7.29	23.4	50	48	86.1	115.2	.....	...
	10	5.44	232.2	194.5	0.84	7.30	24.9	52	54	83.0	113.3	140.4	4.5
	16	5.48	227.1	185.7	0.82	7.36	25.3	42	52	86.4	.....	.....	...
	23	5.30	.....	.....	....	7.37	25.9	43	50	84.1	.....	.....	...
	44	5.76	227.3	184.3	0.81	7.34	25.0	48	59	86.0	.....	.....	...
F. B.	−5	7.94	254.0	220.4	0.87	7.34	28.7	55	...	87.8	.....	.....	...
BSA 1.68	−1	7.87	277.2	231.5	0.83	7.33	27.2	57	68	91.8	95.4	130.5	4.3
	4	6.48	211.6	174.5	0.82	7.31	23.9	47	73	90.6	104.6	135.0	4.0
	7	6.59	206.5	170.4	0.83	7.34	23.3	44	71	94.1	107.4	134.2	4.1
	10	7.70	205.5	172.9	0.81	7.37	20.7	36	79	92.8	108.3	135.6	4.4
	20	8.78	209.0	270.0	0.91	7.31	24.7	51	76	92.6	107.4	138.6	4.8
	35	8.64	316.0	241.0	0.76	7.37	25.1	44	66	90.0	103.6	138.0	3.7
	49	6.10	222.0	177.5	0.78	7.31	25.9	53	60	90.8	103.6	136.0	3.8
F. M.	−2	5.43	227.5	181.0	0.80	7.36	28.5	50	...	70.0	.....	.....	...
BSA 1.52	−1	5.20	225.8	178.6	0.79	7.36	27.1	49	40	71.7	103.7	138.0	3.7
	4	5.46	223.2	175.2	0.78	7.28	19.4	43	52	80.3	110.0	134.6	4.2
	7	6.38	245.3	195.3	0.80	7.31	20.3	42	54	82.6	107.4	133.8	4.2
	11	5.77	200.0	164.0	0.82	7.35	22.6	42	52	81.2	110.1	136.6	3.9
	18	5.74	207.0	172.3	0.83	7.32	21.7	43	55	83.6	109.2	134.2	4.0
I. C.	−29	....	.....	.....	....	7.34	38.9	75	...	69.0	.....	.....	....
BSA 1.58	−7	....	.....	.....	....	7.40	39.7	65	...	62.0	.....	.....	...
	−1	....	.....	.....	....	7.35	37.4	71	...	34.4	.....	.....	...
	3	....	.....	.....	....	7.30	37.6	79	...	54.2	.....	.....	...
	7	....	.....	.....	....	7.19	36.0	97	...	54.7	.....	.....	...
	13	....	.....	.....	....	7.28	34.7	76	...	77.1	.....	.....	....
	21	....	.....	.....	....	7.24	34.9	84	...	58.8	.....	.....	...
	28	....	.....	.....	....	7.15	39.7	117	...	38.7	.....	.....	...

*Received 25 mg./kg./day for 9 days.

measured by the arterial PO_2 and PCO_2, was increased in all cases.

The sixth case (I. C.) was a thirty-three year old woman with severe pulmonary insufficiency due to chronic inactive tuberculosis, an extensive thoracoplasty and contralateral pulmonary emphysema. At the time of the study the patient had been in an Emerson respirator and was receiving nasal oxygen except for a few hours each day for six days. After seven days of administration of diamox (10 mg./kg./day) there was little change in plasma bicarbonate, whereas the pH fell from 7.33 to 7.19 and the PCO_2 increased from 71 to 97 mm. Hg. Arterial blood oxygen saturation also fell sharply during this period. After two to three weeks on the drug regimen a further slight decrease of plasma bicarbonate appeared, the pH increased to 7.28 and the PCO_2 fell to 76 mm. Hg. During this interval the patient was somewhat improved but after about three weeks, despite use of the respirator and the continued administration of diamox, nasal oxygen and supportive measures, the patient lapsed into coma and died. Terminally the pH dropped to 7.15, while the plasma bicarbonate rose to 39.7 mEq./L. and the PCO_2 to 117 mm. Hg. Although the urinary constituents were not measured in this patient, the urine flow from an indwelling urethral catheter remained adequate (850 to 1,700 cc. per day) during the entire period of diamox administration. There was no clinical evidence of renal insufficiency. In this patient, despite apparently normally functioning kidneys, administration of diamox failed to produce a large reduction in plasma bicarbonate. Autopsy revealed extensive pulmonary fibrosis secondary to chronic inactive tuberculosis and chronic pulmonary emphysema. No pathologic changes were found in the kidneys.

Acute Changes. The acute effects of the oral administration of large doses of diamox (25 mg./kg.) on respiratory exchange as well as urinary and arterial blood constituents were observed in five patients with respiratory acidosis. These data are shown in Table III. The response of a typical patient is plotted in Figure 1.

During the first four hours following administration of diamox there was a twenty- to two hundred-fold increase in urinary excretion of CO_2 associated with an increased pH of the urine. In the two cases in which sodium and potassium were studied, potassium excretion was increased significantly and sodium excretion was increased threefold in one case, but decreased in the second case (F. B.). This latter patient also had slightly decreased plasma sodium and chloride, and urinary chloride excretion was also diminished after diamox. In the other three cases there was no significant change in chloride excretion. Urine flow increased in all cases.

A significant decrease in plasma bicarbonate (1.6 to 3.1 mEq./L.) and pH (0.05 to 0.09 pH units) occurred in all patients two to four hours after diamox was given. Whereas no significant change in minute ventilation was noted during the four-hour period, the arterial blood PO_2 increased 11 to 13 mm. Hg. Despite the increase in PO_2, the PCO_2 not only failed to decrease but also actually increased 2 to 4 mm. Hg. There was no significant change in oxygen consumption, carbon dioxide excretion or respiratory quotient. In the two patients examined no significant change in plasma sodium, potassium or chloride was observed.

The fifth case (G. Z.), a patient with long-standing and far advanced pulmonary emphysema and respiratory acidosis, was admitted to the hospital in acute pulmonary insufficiency secondary to an acute respiratory infection. Treatment with antibiotics, bronchial dilators and intermittent positive pressure therapy was ineffectual. After twenty-four hours the patient was placed in an Emerson respirator and was given oxygen by nasal catheter. Despite decreased cyanosis, the patient grew more restless, and on several occasions became pale and clammy with a rapid, weak pulse. Total urine flow from an indwelling urethral catheter during the twelve hours before diamox administration was 64 cc. After oral administration of the drug (25 mg./kg.) urine flow did not increase appreciably and there was no significant change in urinary pH or in CO_2 or chloride excretion. Little change in plasma bicarbonate occurred in the six hours after initiation of diamox, whereas the blood pH fell from 7.26 to 7.15 at three hours, as the arterial blood PCO_2 rose. Twenty-four hours after being placed in the respirator the patient died. His total urinary output was less than 200 cc. during the twenty-four-hour period. Autopsy revealed extensive pulmonary emphysema and fibrosis, cor pulmonale and congestion of the abdominal viscera. The kidneys showed no pathologic changes.

Clinical Observations. None of the patients experienced any changes in symptoms during the four hours following the initial dose of diamox.

TABLE III

ACUTE EFFECTS OF DIAMOX (25 MG./KG.) ON URINE, RESPIRATORY GASES AND ARTERIAL BLOOD VARIABLES IN FIVE PATIENTS WITH RESPIRATORY ACIDOSIS

Patient (age)	Time in Minutes	Urine					Respiratory Gases				Arterial Blood							
		Flow (cc./min.)	pH	CO_2 (μEq./min.)	Cl (μEq./min.)	Na (μEq./min.)	K (μEq./min.)	Ventilation L./min./M² BTPS	O_2 Consumption (cc./min.)	CO_2 Output (cc./min.)	R.Q.	pH	$BHCO_3$ (Plasma) (mEq./L.)	PCO_2 (mm. Hg)	PO_2 (mm. Hg)	O_2 Saturation (%)	Cl (mEq./L.)	Na (mEq./L.)	K (mEq./L.)
J. H. (64)	−60	0.2	5.53	0.08	.....	.....	.....	4.33	301.1	237.2	0.79	7.34	31.21	60	57	86.6	.....	.....	...
	−30	0.48	5.59	0.21	11.6	.....	.....	4.86	311.3	251.4	0.81	7.34	30.35	58	53	85.0	.....	.....	...
	60	2.5	7.59	185.5	18.4	.....	.....	4.38	312.5	238.5	0.76	7.35	30.58	57	50	84.4	.....	.....	...
	120	1.25	7.93	245.0	17.0	.....	.....	4.55	344.6	275.3	0.80	7.32	29.90	60	55	87.4	.....	.....	...
	180	1.17	7.76	202.2	15.9	.....	.....	4.75	309.8	235.4	0.76	7.31	29.67	61	60	88.5	.....	.....	...
	240	0.84	7.76	134.0	10.5	.....	.....	4.58	341.4	265.1	0.78	7.29	29.87	64	63	85.0	.....	.....	...
S. B. (58)	−60	.....	.....	.....	.....	.....	.....	4.84	239.0	196.4	0.82	7.40	31.9	53	43	79.3	.....	.....	...
	−30	3.9	6.90	25.1	301.0	.....	.....	5.12	231.0	179.0	0.78	7.39	32.3	55	42	77.6	.....	.....	...
	60	14.2	7.54	588.0	520.6	.....	.....	5.27	228.0	183.6	0.81	7.39	31.4	53	48	80.0	.....	.....	...
	120	6.0	7.63	436.0	324.0	.....	.....	5.83	230.5	178.2	0.77	7.39	30.9	53	45	82.6	.....	.....	...
	180	8.6	7.59	485.0	349.0	.....	.....	4.92	236.5	183.0	0.77	7.36	30.1	55	52	83.4	.....	.....	...
	240	8.2	7.50	472.0	368.0	.....	.....	4.73	230.3	181.6	0.79	7.34	29.1	56	56	88.8	.....	.....	...
F. M. (41)	−60	0.53	5.44	0.215	52.0	23.5	25.2	5.43	227.5	181.0	0.80	7.37	26.9	48	38	71.8	103.7	138.0	3.7
	−30	1.49	6.09	4.52	143.0	72.9	67.5	5.20	225.8	178.6	0.79	7.36	27.2	50	39	71.5	102.0	137.7	4.0
	60	6.03	7.73	282.0	139.5	276.0	142.5	5.30	224.1	175.0	0.78	7.34	26.4	50	44	70.1	104.6	134.6	3.6
	120	2.28	7.89	234.0	67.7	192.5	110.6	5.94	230.2	183.5	0.80	7.33	24.7	49	50	75.4	104.6	134.2	3.7
	180	2.17	7.95	296.0	73.4	281.0	149.5	5.90	226.0	173.0	0.77	7.27	24.6	55	50	77.2	104.6	134.4	3.7
	240	1.87	7.93	254.0	73.5	273.0	134.0	5.95	228.4	180.0	0.79	7.28	23.9	53	49	76.6	105.5	134.4	3.5
F. B. (61)	−60	0.50	5.64	0.16	40.6	35.7	18.0	7.94	277.2	231.5	0.83	7.38	27.2	47	62	91.8	95.4	130.5	4.3
	−30	0.40	5.76	0.11	.....	.....	.....	7.70	254.0	206.1	0.81	7.39	26.4	45	63	91.4	96.4	128.1	4.4
	60	0.21	8.36	29.5	2.29	8.72	42.5	8.21	268.1	233.5	0.87	7.34	25.0	48	77	96.6	96.4	131.7	...
	120	0.38	8.11	50.5	3.63	6.5	81.0	8.04	236.0	184.5	0.78	7.32	25.3	51	61	90.7	98.2	131.0	4.4
	180	0.47	8.06	64.0	3.26	26.5	88.8	7.91	242.0	193.5	0.80	7.33	24.7	48	73	92.2	96 4	130.3	4.4
	240	0.66	7.86	104.7	2.76	26.6	128.0	8.57	255.8	194.4	0.76	7.35	26.2	49	72	91.8	96.4	131.0	4.3
G. Z. (48)	−60	0.09	5.09	0.03	4.1	.....	.....	.....	.....	.....	.....	7.26	29.3	67	87	93.6	92.0	130.1	4.8
	60	0.67	5.06	0.49	18.3	.....	.....	.....	.....	.....	.....	7.20	28.7	76	84	96.3	.....	.....	...
	120	0.18	5.08	0.08	6.0	.....	.....	.....	.....	.....	.....	7.16	28.5	82	40	67.2	.....	.....	...
	180	0.13	5.01	0.02	2.3	.....	.....	.....	.....	.....	.....	7.15	27.6	82	48	77.7	.....	.....	...
	240	0.15	4.89	0.03	2.8	.....	.....	.....	.....	.....	.....	7.20	27.1	72	66	86.9	.....	.....	...
	300	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.20	28.4	75	82	92.6	.....	.....	...

Of the six patients given diamox continuously for eighteen to fifty-four days, five had been studied extensively over a period of years by repeated physiologic tests to evaluate the effectiveness of other forms of therapy, i.e., bronchial dilators, intermittent positive pressure and pneumoperitoneum; the psychologic effect of the administration of a new drug to these patients was therefore probably minimal. These patients showed slight but real improvement in dyspnea, anorexia and chronic fatigue during the first two weeks of diamox administration. Three of these patients (F. B., S. B. and F. M.) reverted to pre-diamox control symptoms after three weeks of therapy and these have persisted virtually unchanged throughout the period of observation. Patient R. B., after showing some subjective improvement, unaccountably became paranoid after fifty-two days on the drug. There were no changes in blood findings coincident with the change in mental status. Patient I. C. was somewhat improved symptomatically after fourteen days but, despite continued administration of the drug, lapsed into coma and died on the thirtieth day.

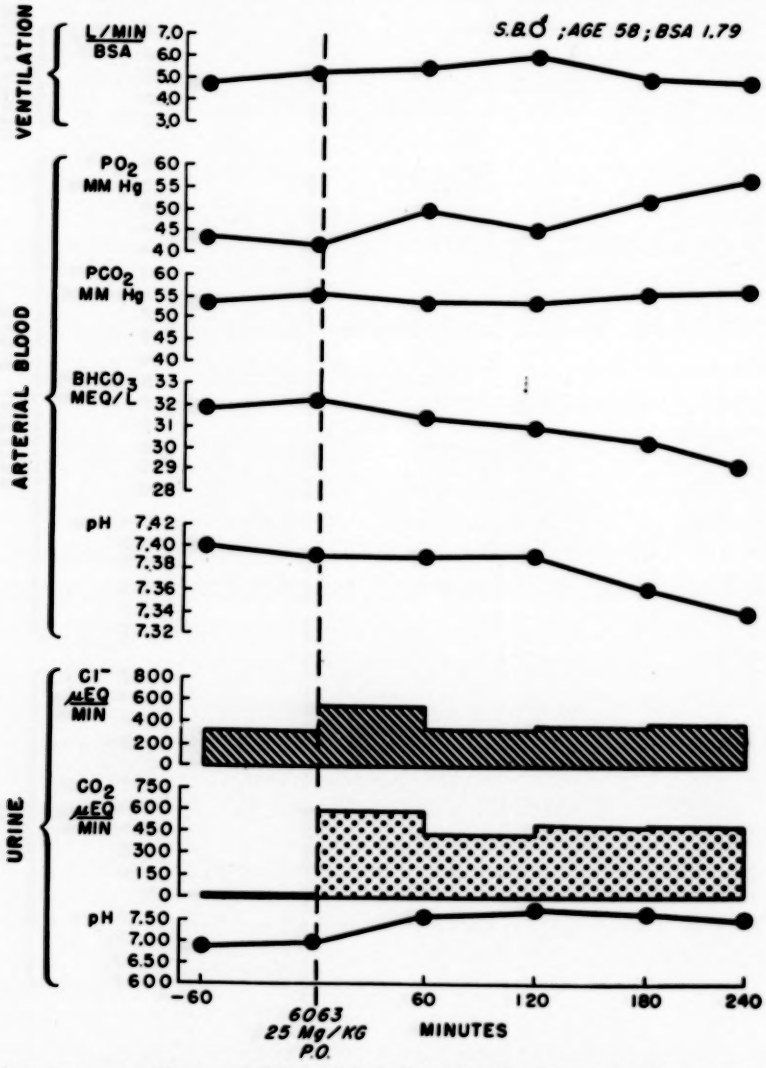

FIG. 1. Acute effects of oral administration of 6063 (25 mg./kg.) on urine, arterial blood and ventilation in a patient with respiratory acidosis.

One patient (J. H.) showed impressive symptomatic improvement, which continued after three weeks of administration of the drug. This patient was a recently discovered and previously untreated case of emphysema. Over the thirty-three-day period of observation this patient expressed dramatic improvement not only in

subjective dyspnea but in his capacity for exertion also. A large psychologic factor in this patient's improvement is probable.

No undesirable side effects from administration of the drug were noted.

DISCUSSION

Most of the sequence of events following the administration of diamox is explained by inhibition of renal carbonic anhydrase activity and has been described by other workers.[1,2,11] Interference with the normal renal carbonic anhydrase activity decreases the hydration of CO_2 and subsequent dissociation of hydrogen ion from carbonic acid. As a result there is: (1) increased sodium excretion due to interference with the tubular exchange mechanism whereby hydrogen ion is substituted for sodium; (2) increased potassium excretion as the "competition" between hydrogen and potassium in the ion exchange mechanism for sodium reabsorption is upset by diamox, and potassium rather than hydrogen is substituted for sodium; (3) increased CO_2 excretion, mostly as bicarbonate, since the bicarbonate in the tubular urine is excreted instead of combining with hydrogen to form carbonic acid with subsequent dissociation into H_2O and CO_2; the CO_2 so formed then normally would diffuse back into the blood; and (4) decreased ammonium ion excretion resulting from less available hydrogen ion to react with ammonia.[12–16] As a result of these changes in electrolyte excretion, copious quantities of alkaline urine are excreted, and plasma pH and bicarbonate are decreased. These effects of diamox were observed in most of our patients with respiratory acidosis. Changes in urinary electrolyte excretion and urine flow were marked within the first four hours after administration of the drug and maximum during the first twenty-four hours. With one exception, urinary flow and electrolyte excretion resumed control levels within the first three days of continued administration of the drug, and no further weight loss as a result of diuresis occurred after this interval. Return of urinary flow and constituents to control levels within the first few days of treatment with diamox has been noted by others,[1,2,11] and this apparent resistance to continued administration of the drug has been shown to persist with doses up to 3.0 gm. per day.[11] However, the serum bicarbonate remains consistently below and the serum chloride above control values, and these values, on discontinuance of the drug, show an appropriate decrease in sodium and potassium excretion. The mechanism of this apparent resistance is not clear. It may be related to the diamox-induced metabolic acidosis. With more hydrogen ions made available in the renal tubular cell by the acidosis, urine acidification mechanisms can operate even in the presence of continued inhibition of renal carbonic anhydrase activity.[17]

In all of the cases in which diamox induced a decreased plasma bicarbonate and pH, a significant decrease in PCO_2 and significant increase in arterial PO_2 followed. These changes were apparent when measured three days after continued administration of the drug in a dose of 10 mg. per kg. per day, and are best explained by improved alveolar ventilation, since the effect of acidosis on the O_2 dissociation curve is insufficient to explain the degree of increased PO_2 observed and the effect of acidosis on blood *per se* cannot account for the concomitant decrease in PCO_2.

Whether the improved alveolar ventilation results from hyperventilation induced by the metabolic acidosis or from improved alveolar ventilation-perfusion relationships occasioned by the fluid loss is not clear from these studies, since no consistent and significant increase in total ventilation was noted in our subjects. However, it is entirely possible that sustained hyperventilation, too subtle to measure by our methods, was effective in reducing the PCO_2 over a period of days. In any event, improved alveolar ventilation after administration of diamox can result without a measurable change in minute ventilation, and has been demonstrated in both acute and chronic experiments. On the other hand, a significant diuresis has occurred in every instance in which improved alveolar ventilation was noted.

Study of the acute respiratory responses to large oral doses of diamox has shed some light on the action of the drug in patients with respiratory acidosis. Within the four-hour period of observation after administration of diamox, a significant drop in serum bicarbonate and pH occurred. During this period a significant increase in arterial PO_2 occurred without a measurable change in total ventilation. The slight but consistent increase in arterial blood PCO_2 was surprising in view of the concomitant increase in arterial blood PO_2. Several explanations for the increased PCO_2 are possible. The effect of

acidosis on the blood alone could account for the increase in PCO_2 but this is unlikely in the presence of increased alveolar ventilation. Moreover, acidosis cannot account for the degree of concomitant increase in PO_2 observed, the latter undoubtedly resulting from increased alveolar ventilation. A rising blood PCO_2 in the presence of increased alveolar ventilation could result from interference with the carbonic anhydrase activity of the red cell by diamox. Evidence in favor of this hypothesis is demonstrated in studies in which alveolar air was sampled by collection of end tidal air.[21] The alveolar PCO_2 so measured was distinctly less than the analyzed arterial blood PCO_2 when measured three and four hours after oral administration of 25 mg. per kg. of diamox to patients with respiratory acidosis. This apparent "PCO_2 gradient" from arterial blood to alveolar air is contrary to all current concepts. Thomashefski and associates[18] found a steep "PCO_2 gradient" from arterial blood to alveolar air after intravenous administration of diamox to anesthetized dogs and concluded that the apparent

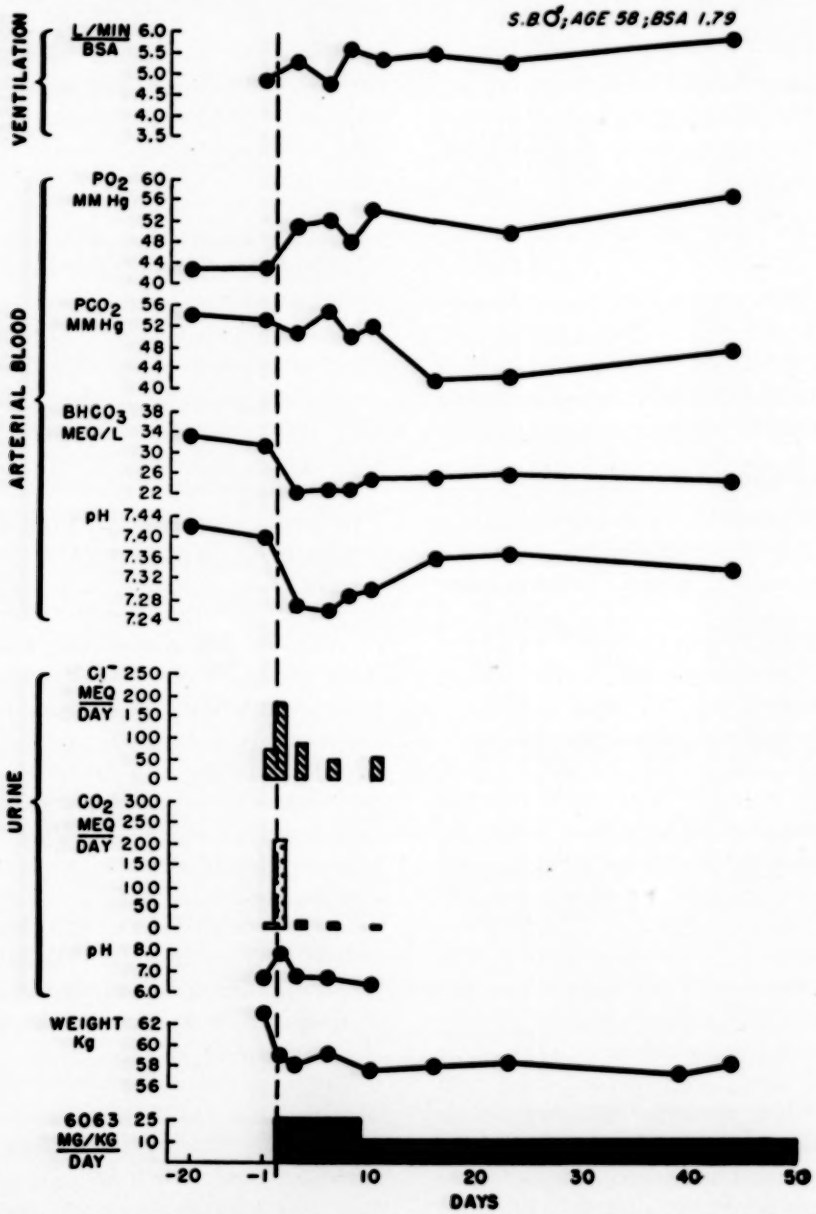

FIG. 2. Effects of continued administration of large oral doses of 6063 (25 mg./kg./day) in a patient with respiratory acidosis.

gradient is probably an artefact, the true *in vivo* pulmonary capillary blood PCO_2 being identical with the alveolar PCO_2. Under the influence of the enzyme inhibitor, release of CO_2 from the red cells to the plasma may be delayed, and in the short time that blood remains in the pulmonary capillary, the plasma PCO_2 could come into equilibrium with the alveolar PCO_2 whereas the PCO_2 of the red cells would remain higher than the plasma PCO_2. By the time the pulmonary capillary blood reaches the peripheral artery and is analyzed, diffusion of CO_2 from the red cell to the plasma is complete and the *in vitro* PCO_2 of the blood would then be higher than the alveolar PCO_2.

This action of diamox, i.e., interference with enzyme activity of the red cell to produce an apparent "PCO_2 gradient" from arterial blood to alveoli, has been observed within ninety minutes after intravenous administration of the drug in a dose of 5 to 100 mg. per kg. to anesthetized and unanesthetized dogs.[18] However, this effect was not observed within two hours after oral administration of the drug in doses of 25 to 50 mg. per kg. to normal dogs or human subjects[18,19] but was noted several hours after large oral doses of the drug in normal exercising man.[20] It is possible that the failure of some workers to observe this "PCO_2 gradient" after oral administration of diamox results from an insufficient period of observation after a large, single dose of the drug. In our patients with respiratory acidosis, inhibition of enzyme activity of the red cell is the best explanation for the slight but consistent increase in arterial blood PCO_2 apparent three to four hours after oral administration of the drug, and occurring simultaneously with increased alveolar ventilation.

That the relative importance of inhibition of enzyme activity of the red cell in determining the blood PCO_2 level may be dependent on the dose of the drug is illustrated by patient S. B. (Fig. 2.) In this case administration of 25 mg. of diamox per kg. per day was continued for nine days, during which there was no significant reduction in PCO_2 despite severe metabolic acidosis and increased alveolar ventilation, the latter indicated by elevation of arterial PO_2. When the dose of diamox was reduced, the PCO_2 decreased and the severe metabolic acidosis improved. With the larger dose of the drug the *in vitro* PCO_2 of the blood remained elevated and essentially unchanged, in spite of increased alveolar ventilation, presumably as a result of inhibition of enzyme activity in the red cell. With 10 mg. per kg. per day inhibition of red cell enzyme activity was apparently less prominent and the PCO_2 was reduced by the improved alveolar ventilation.

Thus it appears that whether the *in vitro* PCO_2 in a given patient is elevated or depressed by diamox is dependent on the balance of the two opposing actions of the drug, one tending to increase the *in vitro* PCO_2 by inhibition of enzyme activity of the red cell and the other tending to decrease PCO_2 by improved alveolar ventilation. Such factors as the size of the dose, the time after the dose that the observations were made and the route of administration seem to be important in determining the degree of interference with enzyme activity of the red cell. The effects of the drug contributing to improved alveolar ventilation, i.e., metabolic acidosis and probably water diuresis, on the other hand, are produced by much smaller doses of diamox than are required to produce significant interference with red cell enzyme activity. Probably it is the net effect of these factors which determines the blood PCO_2 after administration of diamox, and the variability of these factors accounts for the conflicting reports in the literature concerning the effect of diamox on the *in vitro* PCO_2 in normal and diseased subjects.[2–4]

With a single exception (J. H.), the symptomatic response of our patients to diamox has been disappointing. Most of the patients experienced some decrease in dyspnea and chronic fatigue during the first two weeks of drug administration. The clinical improvement was roughly comparable to the chemical improvement described. However, despite continued administration of the drug, most of the patients' symptoms returned to pre-diamox severity after two or three weeks. In these patients the PCO_2 and PO_2 returned toward control values even though the plasma bicarbonate and pH remained below control values. In two severely ill patients diamox failed to produce chemical improvement and failed to alter the fatal course of their respiratory acidosis.

SUMMARY

The effects of diamox on respiratory variables and urinary excretion were observed in seven documented cases of pulmonary emphysema with chronic CO_2 retention.

In most instances diamox induced a copious diuresis of alkaline urine containing large

quantities of sodium, potassium and bicarbonate. With continued administration of the drug the urinary excretion pattern reverted to control values within a few days, but metabolic acidosis (plasma bicarbonate and pH decreased below control values) and the "dry weight" of the patient persisted throughout the period of drug administration.

The administration of diamox resulted in improved alveolar ventilation, as measured by increased PO_2 and decreased PCO_2, after three days of continued dosage. Increase in alveolar ventilation occurred without a consistent increase in minute ventilation but was always associated with significant diuresis.

Increased alveolar ventilation, as indicated by increased PO_2, was noted within four hours after a large oral dose of diamox although the PCO_2 of arterial blood increased during this interval. This elevation of PCO_2 in the presence of increased alveolar ventilation is considered evidence for inhibition of carbonic anhydrase activity of the red cell. The implications of this effect of diamox in patients with respiratory acidosis are discussed.

Most patients exhibited some symptomatic improvement for about two weeks on the drug, followed by return of pretreatment symptoms. In two severely ill patients diamox failed to produce significant improvement in the blood abnormalities and did not alter the fatal course of their respiratory acidosis.

Acknowledgments: The authors gratefully acknowledge the technical assistance of Miss Grace Balzer and Miss Virginia Amburn.

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Spontaneous Irruption of Air from the Lung*

I. Pneumomediastinum

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THE purpose of this study is to review and restudy the mechanisms associated with the spontaneous escape of air from the alveoli of the lung. This discussion will deal with one possible route air may follow after it ruptures through the alveolar wall. Later studies will deal with some of the other possibilities, such as pneumopericardium, pneumoperitoneum and pneumothorax.

The material on which the studies are based consists of sixty cases of spontaneous irruption of gas from the alveolus observed by the author and his associates. In ten of these cases peculiar adventitious sounds near the heart, sounds described as crunching, crackling or clicking, were noted by more than one observer. What was immediately striking was that each of the ten was associated with left-sided spontaneous pneumothorax. It was also noticed that the sounds were quite evanescent in some individuals and that they frequently could be elicited only in the left lateral decubitus, but sometimes in other specific positions. All observers were agreed that the sound was that known as Hamman's sign of mediastinal emphysema, yet there was not a single case of associated subcutaneous emphysema nor an instance of acceptable x-ray evidence of pneumomediastinum. Many of the patients did indeed present in films a line of lucency along the left cardiac border, but no streaks of air could be seen within the mediastinum in any other view.

Certain questions seem to require an answer: (1) Is the crunch pathognomonic of pneumomediastinum? What of other physical signs which are usually considered confirmatory? (2) Why is the crunch so frequently associated with left spontaneous pneumothorax? (3) Is there any good reason why the crunch is so frequently heard in only one position and tends to disappear in others? (4) Is the x-ray sign of lucency along the left cardiac border a satisfactory proof of pneumomediastinum? With these questions in mind it has seemed wise to review the entire problem of the pathology, anatomy and physiology of the mediastinum and to present a number of cases that have come under direct observation.

Anatomy. The standard textbooks of anatomy,[1] although varying somewhat in detail, state that the mediastinum, which is not a structure but only a space, is divided into compartments partly by extension downward of deep cervical fascia and partly by the mediastinal contents themselves. Anteriorly, the superficial layer of deep cervical fascia extends downward from its investment of the sternomastoid muscles to attach to the posterior surface of the sternum, thus constituting the anterior boundary of the superior mediastinum. The middle layer (pretracheal), after extending laterally to form the carotid sheaths and then blending with the fascia of the trapezii, proceeds downward in front of the trachea to insert on and merge with the fibrous layer of parietal pericardium. This layer serves to separate the anterior superior mediastinum from an inferior and more intermediate portion which contains the heart and great vessels and the bronchi. The posterior surface of the parietal pericardium is the anterior boundary of the posterior-inferior compartment, while the deepest layer of deep cervical fascia (prevertebral) continues into the thorax to merge with the endothoracic fascia in front of the vertebral column and to constitute the posterior boundary of the mediastinum. The development of these layers of fascia differs from person to person and the compartments bounded by them are not always airtight. Furthermore, disease, obesity and fibrous thickening from previous inflammation may modify their character considerably.

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The lateral boundaries of the mediastinum consist of the mediastinal pleurae. In their central parts they are perforated by the pulmonary vessels and the bronchi, while below there is a double fold of pleura, the pulmonary ligament, which reaches from the hilum down to the diaphragm. The anterior-inferior portion of the mediastinal pleura is very closely applied to and merges with the fibrous pericardium. The left side of the mediastinum is reinforced by the arch and the descending aorta.

One other point is anatomically of some significance. The adventitia of the pulmonary vessels merges with the outer fibrous pericardium and these vessels invaginate the endothelial pericardium, rather than pierce it. Clinical observations support these anatomic descriptions.[2,3,6]

If air enters the mediastinum from the lung, it must of necessity follow either the bronchi or the vessels. It was Hamman's opinion[13,14] that it might follow either channel but Macklin[11,12] in sections from animals demonstrated that it follows the vessels. That opinion is supported by Tocker and Langston[4] using postmortem human material, which further indicated that air might enter only along the arteries. (It should be noted that the mediastina of most lower animals are comparatively rudimentary and are practically never complete thoracic partitions.) In dissecting along vessels air would clearly enter behind the pretracheal fascia at a level above the heart.

Perforations of the bronchi, trachea and esophagus produce pneumomediastinum (though not a "spontaneous" one). In all of these instances gas enters posterior to the middle layer of cervical fascia. The importance of these relationships is that unless the volume of gas is very large or the pressure very great, air shadows should not be seen anterior to the heart shadow or lateral to the left heart border. Particularly in the latter case only extreme pressure could serve to separate the close attachment of the pleura to the pericardium. If the pressure were quite considerable, however, air might rupture the pretracheal fascia and come to occupy the anterior space.

A rare cause of pneumomediastinum is the escape of therapeutic pneumoperitoneum into the upper structure. The cases of Simmonds[16] and Welty[15] are of this character, though in Welty's case the diagnosis was based entirely on crunch, which as will be shown later might have been misleading. Escape of air from the peritoneum into the mediastinum could take place either about the aortic or esophageal hiatus but possibly also through the foramina of Morgagni and of Bochdalek, subsequently dissecting its way subpleurally toward and into the mediastinum. Probably a more common accident is rupture of pneumoperitoneum directly into the pleural cavity.

In spontaneous pneumomediastinum, however, reviews[17,18] of reported cases indicate discernible subcutaneous emphysema in only about 25 per cent of all cases. On the other hand, in every available report of fatal cases[9,19–24] except those of Jones and Aisner there was subcutaneous emphysema as well as pneumomediastinum. In Aisner's Case 7, that of a newborn infant, air was discovered in the hilum of the lung.

From a theoretic standpoint it would not be necessary that air should always move from the mediastinum into the neck. If expiratory obstruction developed, since the pressure both in the thorax and the peritoneum would be well above atmospheric, the flow of gas should be toward the neck. On the other hand, if inspiratory obstruction was mainly involved, the direction of pulmonary interstitial air should not be toward the mediastinum at all but toward the pleura, in which case, should air already have reached the mediastinum, one might well expect rupture into the pleura. Finally, if both inspiratory and expiratory effort were about the same, air that had reached the mediastinum should tend to remain there.

Pathology. With the exception of a few reports[24,25] most cases of pneumomediastinum that have come to autopsy present rather extensive dissection of air in the form of small vesicles not larger than 1 cm. in diameter.[9,21] It seems likely that in most cases gas tends to be broken up into small bubbles. Such at any rate is the case when air is injected into the hilum of the lung postmortem. After some 200 ml. of air are injected the mediastinum becomes a crepitant mass consisting of numerous small vesicles which do not exceed 1 cm. in diameter. On the other hand, if gas is injected upward behind the xiphoid, larger collections are produced.

Physiology. Since Macklin's original description of "air-lock" and "air-block" resulting from pulmonary interstitial emphysema there have been various efforts to explain the clinical symptoms of dyspnea, cyanosis and circulatory failure. Pressure in the pulmonary veins being very low, it would take a pressure of but a few

cm. of water to interfere with the circulation. Forbes et al.[10] observe, however, that in five years in a very large pediatric service they never observed a single case of pulmonary interstitial emphysema and resultant air lock. Nixon[21] accepts the Macklin hypothesis, as does Wallace.[19]

Various efforts to determine the effect of pneumomediastinum upon the circulation by use of the electrocardiograph have led to no consistent findings.[26–28] It would seem reasonable that disturbances might take place only if the mediastinum were subjected to quite considerable pressure, while in mild cases there might be no evident change in tracings. Animal work[23] indicates that the effect of pneumomediastinum at first is evidenced by the assumption of an inspiratory position, shallow breathing, a fall in intrathoracic pressure and subsequently a fall in peripheral blood pressure.

Nevertheless, patients with what has been diagnosed as pneumomediastinum (as well as those with spontaneous pneumothorax) often manifest acutely a picture of anxiety, sweating and variable fall in systemic blood pressure. Upon bed rest and sedation these patients rather promptly return to a normal status provided excessive positive pressure does not develop.

In more severe cases, when the mediastinum is under great pressure, several mechanisms operate. Respiratory motion is painful, the lungs are displaced and their motion hindered by adjacent swelling of the mediastinum, return blood flow through the venae cavae may be impeded and possibly some of the vagal reflexes become operative. To possible elements of neurogenic shock may be added failure of the thoracic suction pump. If hypoxia then develops, with pulmonary arteriolar constriction, the circulation is likely to fail. If, as in severe cases, there is also spontaneous pneumothorax, the series of events would be accelerated. Available experimental work[23] supports such a concept.

Clinical Diagnosis. Following the original contributions of Hamman, all subsequent reporters of pneumomediastinum have accepted certain criteria which he mentioned. His discussion of the physical examination made the following points: " . . . the presence of the peculiar crunching, crackling, bubbling sounds heard over the heart with each contraction. Often this sound is heard in certain positions, not in others. . . . The area of cardiac dullness may be diminished in extent or replaced by a tympanitic percussion note. . . . The detection of crepitation in the neck makes the diagnosis obvious." Draper,[17] for example, writes, "(The sound) . . . cannot be confused with any other condition, nor does it occur in any other condition." And of the diminished cardiac dullness, he states, "When present this is a virtually pathognomonic sign."

X-ray Diagnosis. The first to suggest that a streak of lucency along the left cardiac border was diagnostic of the condition was Smith in 1918.[29] The next discussions are those of Morey and Sosman in 1939[30] and of Kellogg in 1942[31] who states, "a characteristic parallel line along the left border of the heart" is an indication of pneumomediastinum. Numerous others regard this lucency line as a pathognomonic roentgen sign.[17,24,32–35] Others signs mentioned as diagnostic are unusual definition of aortic knob[36] and the presence of a large lucent area between the sternum and the heart[28,37,39] but Collins warns that the precardiac collection of air may also be due to pneumothorax.[41] Evans and Smalldon[25] in an excellent discussion state that if paracardiac lucency is to be ascribed to pneumomediastinum, streaks of air must be shown within mediastinum limits in other views. In unquestionable cases of pneumomediastinum as determined either by the presence of subcutaneous gas or by postmortem examination they were able to show that paracardiac lucency was present in many instances. They did not observe or comment upon the point that the position of the gas streaks was constant rather than shifting.

COMMENT

Much of the search for and report of cases of pneumomediastinum has arisen from widespread acceptance of the work of the Macklins as demonstrating not one cause but the sole cause of spontaneous irruption of air from the lung. This is a logical necessity if spontaneous pneumothorax is subsequent to and contingent upon pneumomediastinum. But the overwhelming majority of reported postmortems and of surgical specimens point rather to rupture of bullae as the most frequent mechanism.[42]

It seems desirable to review conditions that may be associated with cardiac crunch. The commonest of these is left-sided pneumothorax. The first notes in regard to precordial clicking or tapping are those by Smith,[29] Munden[43] and Rees and Hughes[44] in 1918. All of these writers

describe sounds in association with left-sided pneumothoraces which various writers have accepted as evidence of pneumomediastinum. Horine in 1939[45] described the typical pain ascribed to pneumomediastinum in a young woman with a left spontaneous pneumothorax. The patient described a sensation as though her heart was "flopping around." Visualization of the anatomic fact is very easy in fluoroscopy of patients with left-sided therapeutic pneumothorax and there were complaints of churning in the chest among patients who received that treatment.

The case of Louria in 1939[46] is of particular interest. A patient who had a left therapeutic pneumothorax underwent spontaneous collapse. When the air was nearly all withdrawn there developed a harsh, grating friction rub which was loudest during systole. A second patient with a spontaneous pneumothorax complicating a therapeutic right pneumothorax similarly developed such a sound, which subsequently disappeared as the result of a pleural effusion. These spontaneous pneumothoraces, being of tuberculous origin, could not have been precipitated by the pulmonary interstitial eymphysema mechanism of Macklin but were due to the erosion of a tubercle into the pleura. Yet sounds such as are attributed to pneumomediastinum were encountered.

Scadding and Wood in 1939[47] reported four cases of clicking spontaneous pneumothorax; but, more important, in two of four cases of induced left pneumothorax they heard clicking and crackling sounds. In the case of the induced pneumothoraces the crackling was abolished in the one instance by addition of 150 cc. air on the second day, while in the other 300 cc. of air served to abolish the sound. They ascribed the sound to the forcible separation of the pleurae by an air bubble moved back and forth by cardiac activity, and added that "the clicks have not been heard in association with larger pneumothoraces." These authors believed, as did Greene,[48] that the sounds were probably different in quality from those described by Hamman.

Adcock[49] cites four cases of left-sided therapeutic pneumothorax in which loud, knocking noises were heard soon after induction. But the sound in these is said to have been single rather than of to-and-fro character. Saltzman[50] describes a patient with a left spontaneous pneumothorax who felt pain and then for about fifteen minutes experienced a systolic "rush" which then disappeared.

Nearly all of these instances refer to the left side and it is very evident that when therapeutic pneumothorax was in vogue a good many sounds were heard that might be distinguished with difficulty from those of pneumomediastinum. This was a common experience among physicians who treated tuberculosis. What is more to the point, since under these circumstances there was no question of the chance injection of air into the lung and thence into the mediastinum, many of these sounds were most striking toward the end of the refill period or at the time when the lung was being allowed to re-expand. A similar observation was made by the author in some cases of spontaneous pneumothorax. In these individuals crunching returned as the lung approached complete re-expansion.

In addition to pneumothorax on the left side there are other causes that seem to be associated with peculiar crunching or knocking sounds synchronous with the heart beat. Harrison[51] noted such sounds in an individual with a dilated lower esophagus. If the esophagus was inflated to a certain point the sound appeared, but if it was deflated the sound could no longer be heard. Such sounds have been noted in the chest of a woman with rather marked bullous emphysema of the lingular segment of the left upper lobe. In Welty's[15] case, in which no evidence of air above the diaphragm was found, the crunching sound may have been due to the very high left diaphragm and the associated tense pneumoperitoneum rather than to a leak of gas from peritoneum into the mediastinum. Similar sounds have been encountered in patients with gastric dilatation.

One may conclude that small, loculated collections of gas in the vicinity of the cardiac apex are capable of producing sounds that would be difficult if not impossible for most observers to differentiate from mediastinal crunch.

The disappearance or diminution in size of the cardiac dullness was stated by Draper[17] to be almost pathognomonic. In fact, of course, it is a sign encountered very commonly in left pneumothorax of whatever type, and certainly it is characteristic of bullous emphysema. A dilated stomach or a pneumoperitoneum may cause confusion. It can therefore hardly be regarded as pathognomonic of pneumomediastinum although it might surely be associated with a large one.

1A 1B 1C

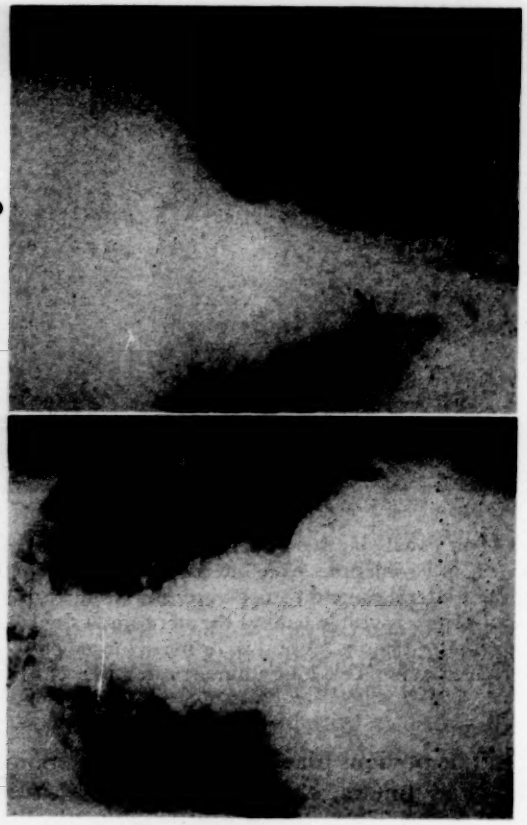
FIG. 1. A, small left spontaneous pneumothorax. Note collection of air chiefly between the left heart border and the lung. No other air could be seen. This case is illustrative of the difficulty sometimes encountered in detecting small pneumothorax. A crunch was heard in certain positions. B, upright lateral same day as Figure 1A. No air can be seen in the mediastinum but a very faint line representing visceral pleura is visible behind the sternum at the level of the second and third ribs. C, left anterior oblique view three days after Figures 1A and B. A line of lucency is seen along the left border of the heart and partly traversing the sternal shadow. This long uninterrupted line of gas is unlikely to be within the mediastinum.

What about the diagnostic significance of a zone of lucency along the left cardiac border? In small pneumothoraces it may be due to trapped air between the lung and the heart. (Fig. 1A.) From habit we have come to expect the largest collection of air to be in the upper portion of the chest. Furthermore we are prone to think of the picture presented by an upright film as representing the constant position of the air. Those who insist upon lateral films have likewise tended to disregard the possibility of shifting of pneumothorax air. The marked changes in the relation of the heart to the anterior chest wall noted by Palatucci and Knighton and by Littman as their patients changed from vertical to horizontal positions seem too great for what might be expected of pneumomediastinum.

If there is one thing that the structure of the mediastinum should indicate, it is that while air may pass through it or remain in it, nothing suggests that gas might shift about *within* the structure. Pneumothorax, on the other hand, shifts about quite readily.

This change in position of air with respect to the mediastinum as the subject changes position could very well explain the fact that crunches and clicks may be heard only under very special conditions of position or respiration. If the source of the clicks were a left pneumothorax, it would be obvious that if the patient lies upon his left side pneumothorax settles against the mediastinum; whereas if he turns to his right side the air lies against the peripheral chest wall, and if he is recumbent gas lies under the anterior chest displacing the heart backward. The opportunity for adventitious sounds in pneumothorax is, therefore, best in the left lateral position. This shifting about of pneumothorax air would explain satisfactorily the frequency of mediastinal crunch in association with left pneumothorax (twelve of twelve cases according to Fagin and Schwab[18] and all ten of the writer's). There is certainly no sufficient difference in the structure of the two sides of the mediastinum to account for a preponderance of rupture of pneumomediastinum into the left pleural cavity. How misleading the crunch may be is indicated by a case[35] of "recurrent pneumomediastinum" which was cured by pleural poudrage bilaterally. If pneumomediastinum were recurring, obliteration of the pleurae would tend to aggravate and intensify the symptoms by preventing decompression into the pleural cavity.

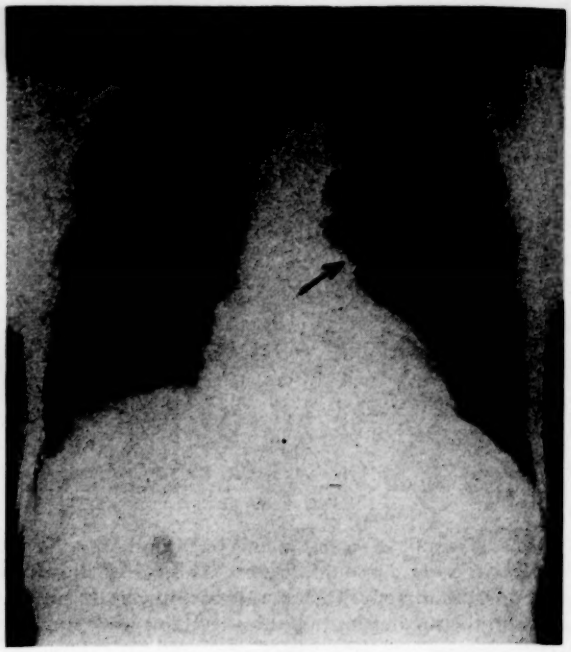
Finally it must be stated that small pneumothoraces around healthy lungs are frequently difficult to see. (Fig. 2A.) The healthy pleura is very thin and could be easily missed if the pleural line happened to follow a rib. There may



1D

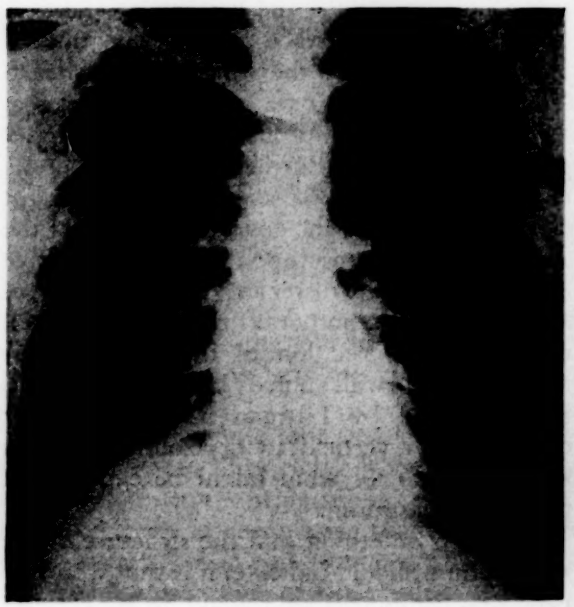
1E

FIG. 1. D, in left lateral decubitus position air is plainly seen lying along the mediastinum above the pulmonary segment. E, in right lateral decubitus position the air has shifted away from the mediastinum and now lies against the lateral wall of the chest at the level of the anterior third, fourth and fifth ribs.



1F

FIG. 1F. Film at expiration, upright postero-anterior view; the only visible air lies along the left cardiac border below the pulmonary vessels.



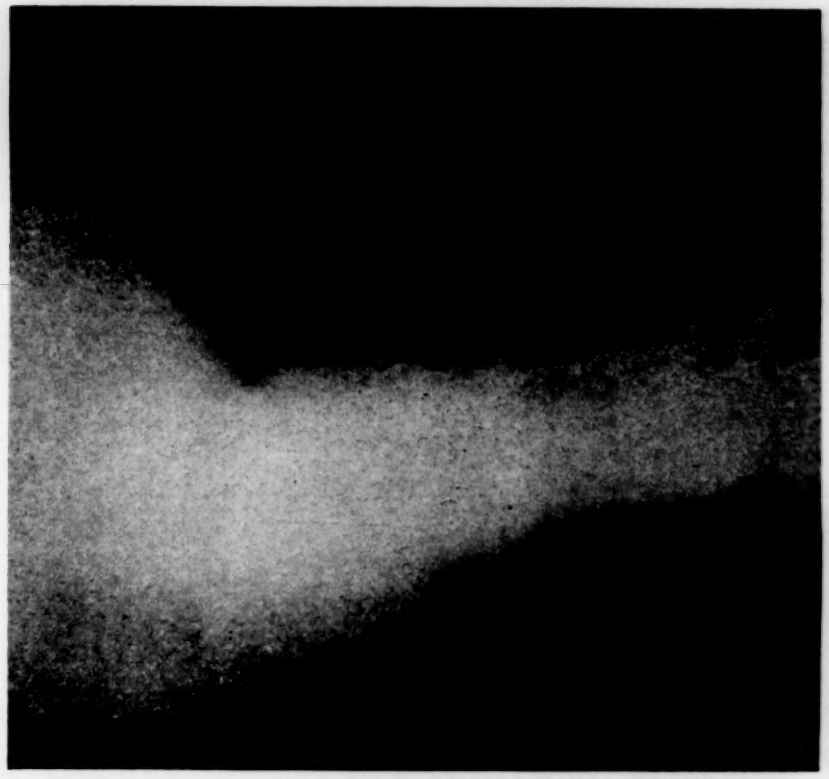
2A

FIG. 2A. A left-sided spontaneous pneumothorax. Postero-anterior upright view shows collection of air to be lateral and superior.

be little difference between the density of the deeply inflated healthy lung and a small margin of air.

For all of these reasons it seems desirable, when one is confronted by a suspected pneumomediastinum, whether the sign be crunch or paracardiac lucency, to carry out a series of maneuvers which will quite adequately exclude confusing causes of such signs. The maneuvers (Figs. 1 and 2) are as follows: (1) An upright, postero-anterior film at expiration; (2) with beam directed horizontally, films made at expiration with the patient in both lateral decubiti; (3) if it seems desirable, films at expiration, the beam being directed horizontally, in the dorsal decubitus. Lateral or oblique upright films may also be of use.

Among forty-seven cases collected from the literature[20,28,35,37,38,42,48,57,58] left pneumothorax was recognized as being present in about one-half. A single frontal film was the basis for diagnosis in sixteen instances. In twelve instances diagnosis was based upon the observation of crunching or clicking alone, while of the entire forty-seven only six presented detectable subcutaneous crepitation in the neck.



2B

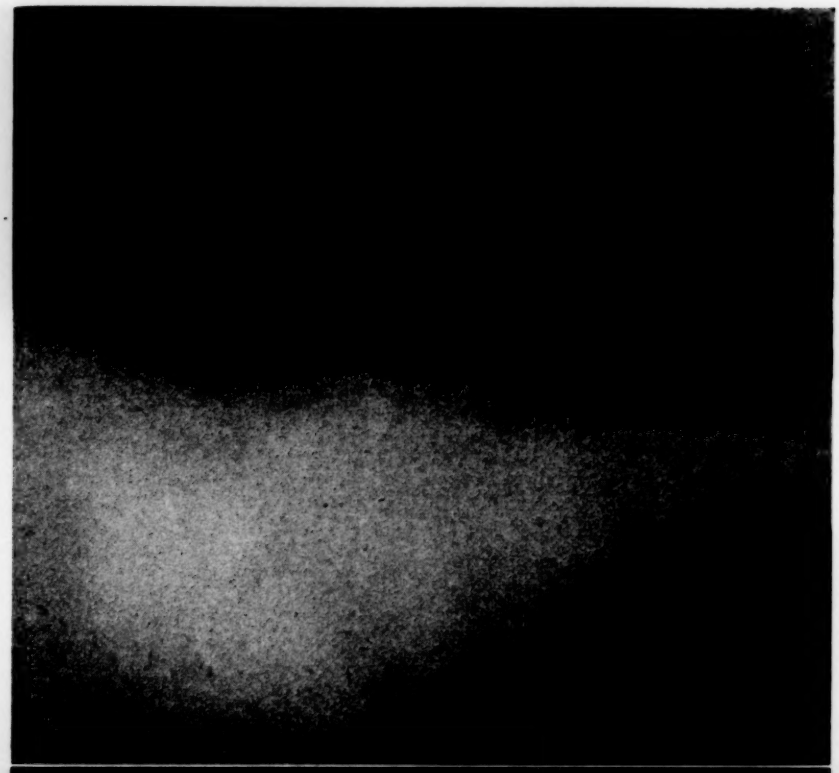
FIG. 2B. Left lateral decubitus view of same patient as in Figure 2A. Air has collected along the mediastinal pleura. A crunch was audible only in this position. Notice how a small layer of air separates the lung from the cardiac apex.

In contrast is the large collection of cases of secondary pneumomediastinum.[3,10,21–25,34,59] Most of these were in children but a fair number were in adults who had asthma, pneumonia, severe cough or some other basic pathologic condition. In this group air was much more readily demonstrated in the mediastinum, subcutaneous emphysema was present in a large majority of cases and in a few decompression of the mediastinum became imperative. These cases represent examples of the Macklin mechanism and are undoubtedly instances of pneumomediastinum.

Contrasted with this variable behavior of pneumothorax are the films (Fig. 3) of the only patient with proven pneumomediastinum who was encountered during the collection of some sixty cases of pneumothorax. The patient, a resident in surgery, noticed the sudden onset of retrosternal pain, followed by considerable pain on swallowing. After some thirty minutes, during which the site of maximum pain became steadily higher within the thorax, he noted also marked difficulty in breathing and a sense of pressure on the trachea. At this point he palpated his neck and detected crepitus. Thereupon he went to the x-ray department and films were made. The following day there was no crunch and the supraclavicular crepitation had disappeared. All air streaks likewise had disappeared within two days.

On the basis of the possibility of confusion of physical and x-ray signs it seems well to require certain criteria for diagnosis of pneumomediastinum: (1) The development of subcutaneous emphysema about the neck is certain evidence of pneumomediastinum if there is no source of air leak in the neck itself. (2) Roentgen demonstration of gas within the borders of the mediastinum may be taken as certain evidence, but a paracardiac or precardiac (lateral view) lucency alone is not sufficient. Such signs call for the maneuvers described to exclude left pneumothorax. (3) The detection of a crunch is not sufficient evidence for a diagnosis of pneumomediastinum unless examination excludes pneumothorax or other conditions which might produce the sound. (4) In the presence of pneumothorax (usually left) a reliable diagnosis can be made only upon the first two points. (5)

2C



2D

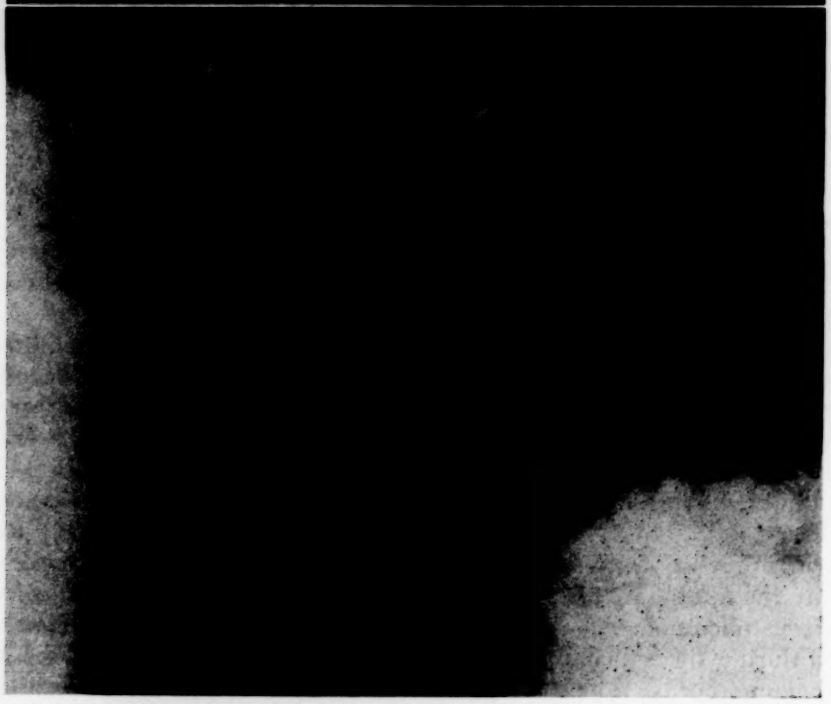
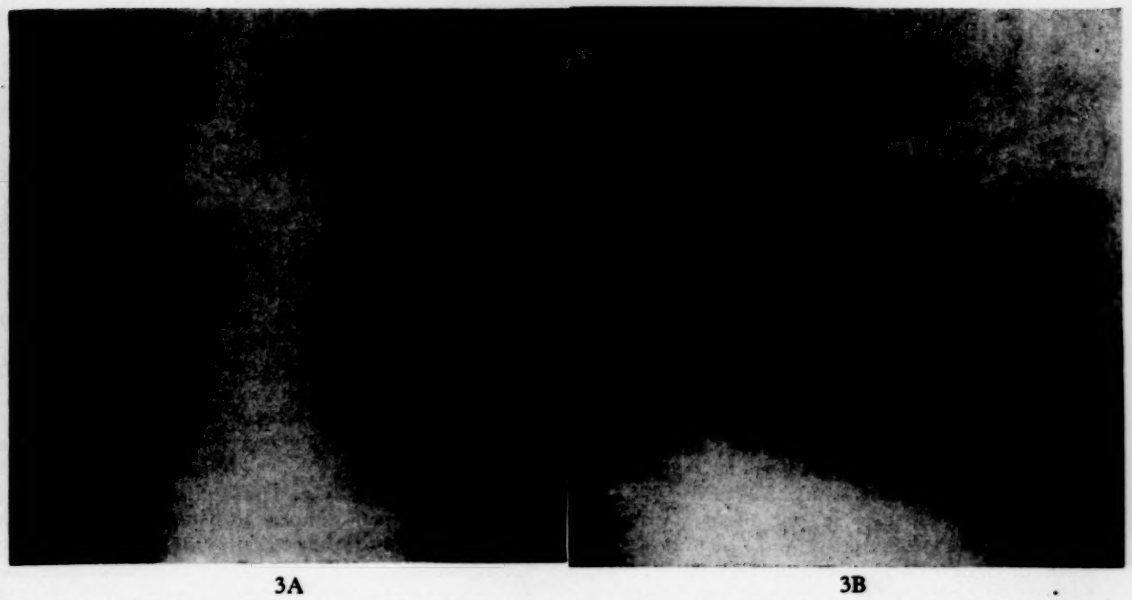


FIG. 2. C, right lateral decubitus view of patient seen in Figures 2A and B. The air has shifted away from the heart to the lateral chest wall; border of lung is barely visible and its position is indicated by pointers. D, same patient in supine position. The pneumothorax air now lies anteriorly in front of the heart and the lung border can hardly be seen except where it crosses the heart shadow.



3A 3B

FIG. 3. A and B, case of pneumomediastinum described in text. Pointers indicate vertical streaks of air dissecting upward around the trachea and in the anterior mediastinum; postero-anterior and lateral views reveal relationships.

Diminution or disappearance of cardiac dullness, with or without crunch, calls for exclusion of pneumothorax, localized or generalized emphysema, or an abnormally high left diaphragm with overlapping gastric or pneumoperitoneal tympany.

SUMMARY

1. The anatomy of the mediastinum is reviewed.

2. The pathology and physiology of pneumomediastinum are reviewed, and experience in the inflation of the mediastinum of fresh cadavers is cited.

3. Possible sources of confusion in diagnosis are considered.

4. Positional roentgenography for the exclusion of pneumothorax is discussed.

5. Criteria for accurate diagnosis are listed.

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Relapse after Pulmonary Resection during Prolonged Streptomycin-Para-aminosalicylic Acid Treatment of Pulmonary Tuberculosis*

An Analysis of Nine Relapses in Eighty-two Cases

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THE introduction of combined streptomycin (SM)-para-aminosalicylic acid (PAS) treatment in 1948 to 1949 has played a great part in reducing the risk of pulmonary resection for tuberculosis. Sufficient experience has now accumulated to permit definition of some of the causes of occasional failure of this now widely accepted treatment.

MATERIAL

Between June, 1949, and June, 1953, 331 patients were started on a regimen of SM and PAS, and this treatment was continued for three to thirty-six months, with an average of fifteen months. Only eighty-two received less than twelve months of treatment. Most received SM, 1 gm. intramuscularly twice weekly, and sodium PAS, 12 to 16 gm. by mouth daily. All but twenty-five had completed their SM-PAS treatment by June, 1954. All received rest therapy, eighty-nine pneumoperitoneum and thirty-three thoracoplasty. Socio-economic factors in these patients were favorable. Contact was maintained to June, 1954, in 98 per cent. A report on the results in the whole group has appeared elsewhere.[1]

Eighty-two of the 331 patients were subjected to pulmonary resection; forty-four of them had closed lesions at the time of operation. To date, eleven have relapsed at some time after the resection. Of these, two were seriously ill at the time of operation; one has since died. These two were the only patients in the series who had undergone pneumonectomy; both had SM- and/or PAS-resistant organisms in the sputum at the start of their *re*treatment before surgery. They will not be considered further in this report.

ANALYSIS

Nine relapses are described. Five of these were receiving SM-PAS therapy for the first time (*original* treatment). (Table I.) Four were receiving SM-PAS *re*treatment (Table II); SM- and PAS-susceptible organisms were isolated from cultures before retreatment in three of these; in the fourth all cultures were negative immediately before and during retreatment. The clinical details before resection, the tissue bacteriologic findings and clinical features of each relapse are outlined in the tables.

All had new roentgenographic shadows at the time of relapse. All except one have responded well to treatment for the relapse. The exception (S. R.) continues to have cultures consistently positive for Mycobacterium tuberculosis three years after his first resection.

Six observations are noteworthy: (1) in eight of the nine cases relapse was characterized by the new appearance of abnormal shadows at or near the site of operation. The ninth relapse was a pleural effusion on the side of operation. (2) Four of the nine relapses occurred after termination of chemotherapy which had been given for more than twelve months, only one of these on

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TABLE I

RELAPSE AFTER PULMONARY RESECTION DURING PROLONGED ORIGINAL SM-PAS TREATMENT OF PULMONARY TUBERCULOSIS: ANALYSIS OF 5 CASES

Case	Preoperative Observations					Tissue Bacteriology				Total Chemotherapy (mo.)	Mo. to Relapse after End of Chemotherapy	Relapse Findings			
	NTA Cl.	Cavities	Sputum Bacteriology		Preop. Chemotherapy (mo.)	Smear	Culture	GP	Susc.*			Site	Cavities	Bact.	Susc.*
			Culture	Susc.*											
B. W.	Min.	0	+	Susc.	1	−	−	−	−	3	8	Same	+	+	Susc.
R. G.	M. A.	Cl.	0	−	1	+	+	−	−	3	30	Same	0	0	−
S. R.†	M. A.	Cl.	0	Susc.	(a) 5 (b) 7	+ +	+ +	+ +	Susc. Susc.	7	During During	Same Same	+ +	+ +	Susc. Susc.
P. H.	Min.	0	0	−	2	+	0	0	−	10	10	Same side‡	0	0	−
W. N.	M. A.	0	0	Susc.	6	+	+	+	SM-susc. PAS-res.	12	8	Same	0	+	SM-susc. PAS-res.

Key: Susc.—Susceptible or susceptibility
Res.— Resistant
0—None or negative
Cl.—Closed
+—Present or positive
−—Not done
Min.—Minimal
M. A.—Moderately Advanced
GP—Guinea pig inoculation
NTA CL.—National Tuberculosis Association classification

* Pretreatment susceptibility: For the purpose of this analysis, streptomycin and PAS resistance are defined as follows:

Streptomycin-resistance: (a) Direct test (A.T.S. solid medium): significant growth in the tube containing approximately 3.5 μg./ml. in comparison to control tube. (b) Subculture test (liquid medium): significant growth in 2.5 or more μg./ml. of liquid Tween-albumin medium observed for fourteen days.

PAS-resistance: Direct and subculture tests (A.T.S. solid medium): significant growth in the tube containing approximately 1.0 or more μg. PAS/ml. in comparison to control tube.

† Two resections, same side.

‡ Pleurisy with effusion only.

TABLE II

RELAPSE AFTER PULMONARY RESECTION DURING PROLONGED SM-PAS RETREATMENT OF PULMONARY TUBERCULOSIS: ANALYSIS OF 4 CASES

Case	Preoperative Observations					Tissue Bacteriology				Total Chemotherapy (mo.)	Mo. to Relapse after End of Chemotherapy	Relapse Findings			
	NTA Cl.	Cavities	Sputum Bacteriology		Preop. Chemotherapy (mo.)	Smear	Culture	GP	Susc.*			Site	Cavities	Bact.	Susc.*
			Culture	Susc.*											
G. K.	M. A.	Open	0	Susc.	4	+	+	+	Susc.	16	10	Same	+	+	−
F. W.	M. A.	Open	0	−	16	+	+	+	−	22	4	Same	+	+	SM-susc. PAS-res.
A. O.	M. A.	Open	+	Susc.	3	+	+	+	Susc.	8	13	Same	+	+	SM-res. PAS-susc.
S. W.†	M. A.	Open Open	0 0	Susc.	5 8	+ +	+ +	+ +	SM-susc. PAS-res. SM-susc. PAS-res.	13	During	Same	+	+	SM-res. PAS-res.

* See Footnote Table I.

† Bilateral resection.

original treatment. (3) The five relapses in patients on original treatment occurred after resection without roentgenographic evidence of cavity and with negative cultures at that time. The four relapses in patients on retreatment occurred following resection, with roentgenographic evidence of cavity at that time, incidentally confirmed in each case by morphologic examination. (4) Two of the relapses occurred immediately after resection during chemotherapy, one of them (S. R.) on original treatment from whose resected tissue drug-susceptible organisms were isolated. (5) In seven of the eight examined relapses occurred in patients whose resected tissue contained viable tubercle bacilli. The one exception was the specimen from the patient whose relapse consisted of a sterile pleural effusion. (6) Organisms susceptible to both SM and PAS were recovered from the sputum at the time of relapse in three of the four original treatment cases in whom data were available; in all three retreatment cases so examined, organisms resistant to SM and/or PAS were recovered from the sputum at relapse.

Reviewing all eighty-two patients who had had resection, viable organisms were recovered from the tissue of seventeen of forty-five original treatment cases (38 per cent) and from twenty-one of twenty-five retreatment cases (84 per cent) so studied. The mean duration of SM-PAS treatment before operation in these cases was as follows: original treatment non-viable organisms, 6.7 months; original treatment viable organisms, 5.6 months; retreatment non-viable organisms, 7.3 months; retreatment viable organisms, 6.3 months. In addition, 25 per cent of lesions from patients who had no roentgenographic evidence of cavity and had negative cultures at the time of resection yielded viable organisms; on the other hand, 60 per cent of lesions from those with open cavity and/or positive cultures at operation yielded viable organisms.

Resection was performed within the first three months of SM-PAS treatment in seventeen of the eighty-two patients, nine of whom still had open cavity and/or positive cultures at the time. There was no evidence in this small series that these patients suffered more complications than those having operation between the fourth and sixteenth month of chemotherapy with approximately the same proportion of open lesions and preoperative positive cultures.

COMMENTS

Since in each case the disease became active again at or near the operation site, it is suggested that the surgeon's knife may have been in part responsible for the relapse. This possibility is supported by the occurrence of relapse immediately after resection in patients S. R. and S. W. during continued chemotherapy. Organisms from the tissue of one (S. R.) were found to be SM- and PAS-susceptible. Patient R. G. is also of interest in this connection. He had bilateral disease at the outset, worse on the left. All the visible and palpable disease on the left was resected. Endobronchial disease was found microscopically at the margin of the resected specimen. Relapse occurred at the site of operation and not on the opposite side. The total of only three months' chemotherapy doubtless contributed to failure in this case.

Potentially dangerous visible and palpable lesions may be removed at the expense of damaging adjacent lung containing invisible and impalpable lesions. This damage may reduce the ability of the lung to hold this remaining disease in check. In short, if living tubercle bacilli are found in resected tissue, they may also be left behind.

The inadequacy for most patients of less than about twelve months' SM-PAS treatment is now well recognized. Relapse in four patients (B. W., R. G., P. H. and A. O.) may be explained at least in part on this basis. The five patients who relapsed during or after *original* chemotherapy (Table 1) were all free of cavity by planigram at the time of operation. On histologic examination a filled cavity was found in one (S. R.) and no cavity was found in the other four. They were selected for surgery at a time when views on surgical treatment were rapidly changing. In retrospect, none of them would be selected for resection at Trudeau Sanatorium today.

Experience to date does not support the theory that a large lesion is more dangerous than a small one.[2]

In addition, there is no evidence as yet that lung resection influences favorably the incidence of relapse in patients with closed lesions during the first three years after completion of twelve months or more of original SM-PAS treatment.[1-3] Under competent SM-PAS treatment the operation is quite safe in most cases, but the indications for operation should be *necessity* and not *safety*. Theoretic considerations about the

potential danger of residual necrotic foci, bronchial communication and possibly viable tubercle bacilli in the tissues should not lead us to interfere with natural healing when clinical experience fails to provide support for our theories.

When is surgery necessary? It is obviously necessary to remove that great mechanical impediment to healing, the persistently open cavity, from which, sooner or later, drug-resistant organisms will probably emerge. Fifty-eight per cent of so-called "open negative" cases have relapsed after completion of twelve months or more of original SM-PAS treatment without resection.[3] Culture conversion and cavity disappearance, if they are to occur, will probably do so by the fourth to the sixth month of SM-PAS original or retreatment, with pneumoperitoneum used in those with cavities of 2 cm. or more.[1] Therefore, in original treatment cases the final decision to resect or not to resect should usually be made by about the sixth month. It will be interesting to discover whether the risk of operative complications and later relapse will eventually prove to be greater in those with closed lesions and negative cultures who are subjected to resection than in those whose lesions are left *in situ*.

Furthermore, this experience suggests that patients receiving SM-PAS *re*treatment with open cavities are in greater danger from resection than are original treatment patients with cavity. This may be due to more rapid emergence of drug resistance during SM-PAS retreatment than during original treatment, an observation whose significance increases as operation is delayed.

SUMMARY AND CONCLUSIONS

1. The clinical details of nine relapses after pulmonary resection performed during prolonged SM-PAS treatment are reported.

2. Relapse in each instance was localized at or near the site of operation.

3. Inadequate duration of chemotherapy and the creation of a favorable environment for the growth of tubercle bacilli by operative tissue damage were felt to be related causally to these relapses.

4. The selection of cases for pulmonary resection during prolonged combined SM-PAS treatment should be based upon clinically demonstrated necessity rather than upon the immediate safety of the operation.

5. Where otherwise indicated and feasible, there appears to be reason to resect *early* in the course of SM-PAS *re*treatment.

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The Superior Vena Cava Syndrome*

Therapeutic Considerations

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The dramatic appearance and acute onset of obstruction of the vena cava is a powerful stimulus to the clinician to begin early treatment. As a consequence, various forms of therapy have been promptly employed and good results have been frequently reported[1–4] in attempts to offer symptomatic improvement to the patient and to cause regression of the basic lesion with restoration of more normal blood flow. These therapeutic measures have included surgical exploration and relief of the obstruction by mechanical means, radiotherapy and chemotherapy with mechlorethamine hydrochloride (mustargen®) and triethylenemelamine, each method used alone or in combination with others. When the reports are reviewed, however, there is some question as to the actual effects of treatment upon the occluded vessel.

Doubts as to the rationale of the methods of treatment in use are based upon the sequence of events following all forms of venous occlusion under any circumstances. The natural establishment of collaterals will in itself serve to give considerable relief of symptoms in the area drained by the obstructed vessel. This occurs no matter what the cause of the original block and even though persistence of the obstruction can still be demonstrated after the improvement occurs. Review of the literature and personal experience indicate that treatment cannot be evaluated by symptomatic improvement or superficial observations alone. The effectiveness of treatment in this syndrome can be determined only by subsequent visualization of the involved vein. This can be achieved during life by phlebography or postmortem by necropsy.

MATERIALS AND METHODS

This paper deals with twenty-one patients with obstruction of the superior vena cava who have been treated by most of the methods previously mentioned. Methods of study included symptomatic follow up, venous pressure changes, phlebography when applicable, and postmortem findings or postimprovement phlebograms. Since the more radical forms of therapy are used almost exclusively in patients with malignant disease, we shall devote ourselves mainly to those with infiltrative tumors. Of the twenty-one patients studied in detail, nineteen had infiltrative tumors of which eighteen were bronchogenic carcinoma; the remaining patient had a malignant thymoma. The two other patients had luetic aortic aneurysms. All of the patients except one showed the features of the syndrome which have previously been described in detail elsewhere.[5] Briefly, they included: (1) Elevated venous pressure in the upper portion of the body with a normal venous pressure in the lower extremities; (2) ruddy cyanosis of the face and neck; (3) edema of the face, neck and arms and (4) moderate to marked collateral circulation.

CLINICAL AND PATHOLOGICAL FINDINGS

Excluding the two patients who died early and in whom treatment is difficult to evaluate, seventeen patients with obstruction caused by infiltrative tumor were extensively treated with chemotherapy or x-ray. (Tables I and II.) Of these seventeen patients six showed marked improvement manifested mainly by decreased swelling of the face and upper extremities, diminution or complete disappearance of cyanosis, return of ability to lie flat, disappearance of headache, fall in the venous pressure usually to normal levels and some decrease in distention of the collateral veins. The most rapid response after initiation of therapy was three weeks, as occurred in two patients. However, studies

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demonstrated that the primary block persisted despite marked improvement. In five, gross necropsy revealed complete obstruction of the vein due to infiltration of its wall. In three of the individuals the tumor filled the lumen. In all cases the return flow of blood was completely obstructed in the superior vena cava. In the one surviving patient phlebograms confirmed persistence of the obstruction.

TABLE I

PATIENTS WHO SHOWED DEFINITE OBJECTIVE EVIDENCE OF IMPROVEMENT SUBSEQUENT TO THERAPY*

Case No.	Evidence That Block Persisted
1	At necropsy the vena caval wall was involved by tumor, with complete stenosis just above the origin of the azygos vein
2	At necropsy there was infiltration of the vena caval wall by tumor, with complete stenosis along its course to 0.5 cm. from the right auricle
3	At necropsy the vena cava was completely surrounded by tumor tissue, with infiltration and complete stenosis of the vessel above the azygos orifice
4	At necropsy the vena cava was infiltrated and completely obstructed along its course to a point 4 cm. from the right auricle, just above the azygos
5	At necropsy the vena caval wall was infiltrated by tumor and puckered to complete obstruction just below the junction of the innominates
6	Postimprovement phlebograms confirmed the presence of complete obstruction below the junction of the innominates, with most of the return flow shunted through the azygos
7	At necropsy the vena caval wall was infiltrated by tumor; the lumen was completely obliterated by organizing clot and tumor

* Improvement was manifested by decrease in swelling and cyanosis, fall in venous pressure to normal, ability to lie down and decreased venous distention.

A seventh patient had no symptoms and no objective evidence of vena cava obstruction during life. Death resulted from massive hemorrhage into the trachea which had been eroded by tumor. At necropsy the vena cava was completely surrounded and infiltrated by tumor. Microscopic sections showed almost complete obliteration of the lumen by organizing thrombus intermingled with nests of tumor cells. One wall of the vessel was infiltrated by tumor cells. Marked intimal thickening was noted.

An additional ten patients energetically treated with x-ray, generally using doses of 4,000 or more roentgens, mechlorethamine hydrochloride (mustargen) in doses of 25 or more mg., and triethylenemelamine in doses of 20 or more mg. showed no improvement whatsoever, although they were followed for at least three months. The method of treatment of the unimproved group did not differ from that of patients who responded favorably. Many of the patients had combined therapy and some had all forms listed. Three of the ten patients showed continued progression of the syndrome despite treatment. At necropsy all of the patients except one had obstruction due to infiltration of the venous wall by tumor tissue. In the one exception the pathologist described obstruction by compression of the superior vena cava by a large mass of lymph nodes involved by tumor. Unfortunately, no sections were taken through the vessel so that the relationship of the tumor to vessel wall was not precisely determined. In all instances in which the histology of the obstruction was studied it was obvious that the tumor responsible for the obstruction had invaded from the neighboring lymph nodes and was actively proliferating within the wall of the vein.

TABLE II

PATIENTS IN WHOM THE CAVAL SYNDROME WAS UNRELIEVED OR PROGRESSED DESPITE THERAPY*

Case No.	Result
1	Syndrome progressed despite radiotherapy, nitrogen mustard and triethylenemelamine
2	Syndrome persisted despite nitrogen mustard
3	Syndrome persisted despite radiotherapy
4	Syndrome persisted despite radiotherapy
5	Syndrome persisted despite nitrogen mustard and radiotherapy
6	Syndrome persisted despite nitrogen mustard and radiotherapy
7	Syndrome persisted despite nitrogen mustard and radiotherapy
8	Syndrome persisted despite nitrogen mustard and radiotherapy
9	Syndrome progressed despite nitrogen mustard therapy
10	Syndrome progressed despite radiotherapy

* Radiotherapy included at least 4,000 roentgens to the mediastinum; nitrogen mustard consisted of at least 25 mg.; triethylenemelamine consisted of at least 20 mg.

Two patients died before treatment could be initiated. Both had bronchogenic carcinoma. Death in one was a direct consequence of vena

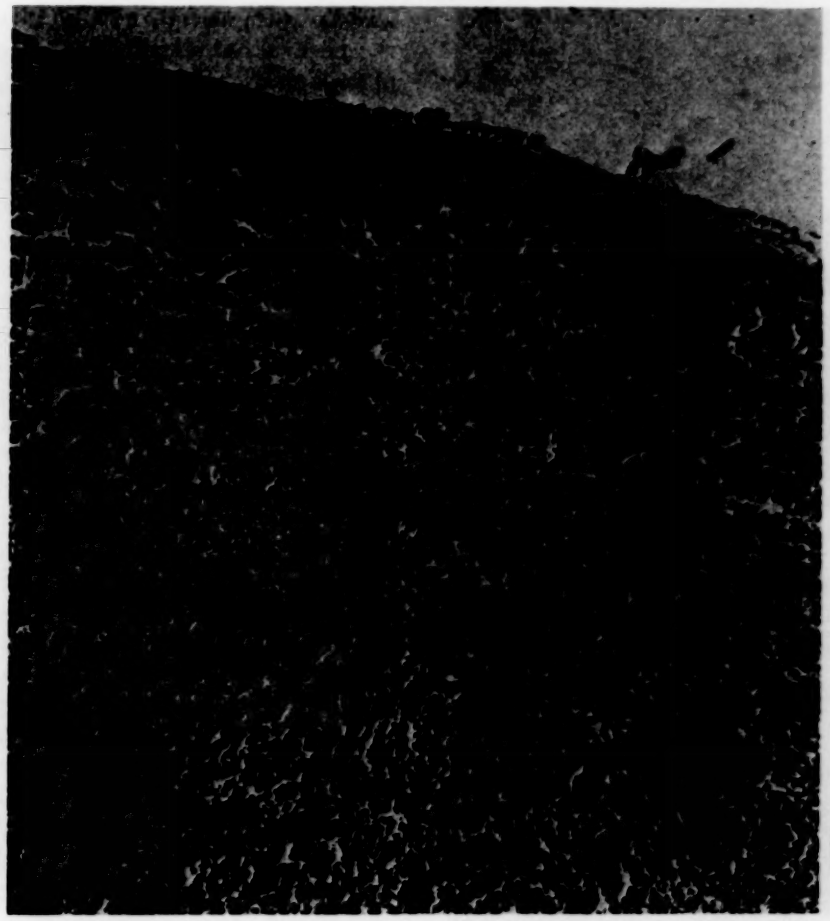

FIG. 1. Section of the superior vena cava showing infiltration by tumor cells throughout the entire wall; × 60.

caval block. The patient had marked venous hypertension and bled profusely from his nose. He asphyxiated from massive aspiration of blood. In the other patient the vena caval block was only one feature of extensive mediastinal involvement. Death resulted from tracheal compression by masses of mediastinal nodes. In both individuals the tumor had invaded the wall of the superior vena cava and had greatly narrowed the lumen.

In the seventeen patients in whom treatment was completed the average life span following the onset of caval obstruction was nine months. Sixteen patients died as a result of progression of the primary malignant disease. One patient is still alive but has cerebral metastases. Only the two untreated patients died within a month after the obstruction occurred; one death was a direct complication of the superior vena cava obstruction.

Phlebograms were obtained in five patients and demonstrated the location of the block as well as the collaterals. They also provided suggestive or confirmatory evidence as to the nature of the block. Seventeen of the nineteen patients presented themselves initially with obstruction of the superior vena cava. The obstruction developed following therapy in the remaining two patients.

There are two patients with aneurysms of the ascending aorta in this series. One patient is still alive after five years of observation. During this period he improved symptomatically but the collaterals have persisted and the venous pressure is still elevated. The second patient died two months after the onset of osbtructive symptoms but there had been marked objective improvement without treatment. Death resulted from spontaneous perforation of the aneurysmal sac leading to massive hemorrhage into the pleura. At necropsy the vena cava was obstructed completely by pressure of the aneurysmal sac. There was one thin adhesion which united the anterior and posterior walls of the

FIG. 2. Gross view of the superior vena cava showing the marked narrowing and puckering of the vessel due to tumor. The vessel has been opened and spread apart.

vein and the intima showed phlebosclerosis of the area in apposition to the aneurysm.

COMMENT

In obstruction due to *neoplastic infiltration* of the superior vena cava the tumor invades the wall and thus occludes the lumen. This obstruction is the result of puckering or stenosis of the vessel; a thrombus is usually associated which frequently contains tumor. Necropsy studies have revealed that this type of obstruction is not relieved despite intensive treatment. Therefore, any improvement which occurs is due to the natural sequence of events in the formation of collaterals. (Figs. 1 and 2.) Interestingly, one patient in our series never manifested symptoms or signs of obstruction during life but complete obstruction of the vein was found at necropsy. The organized thrombus found within the lumen is sufficient evidence that the block had been present for some time prior to death.

In obstruction due to *compression* there is mechanical pressure on the venous wall causing the obstruction of the blood flow. The wall itself is not involved and the lumen is generally patent unless secondary thrombosis has occurred. Elimination of compression by appropriate therapy will relieve the obstruction unless there is a secondary thrombosis. This group includes aneurysms amenable to surgery, constricting bands, and may include specific inflammatory processes such as tuberculous mediastinal adenitis. It is possible that certain lymphomas may produce occlusion by pressure but we have not encountered a case of this sort.

The rare patient with primary thrombotic obstruction will follow a natural course. Occasionally, recanalization of the thrombosed vessel will occur. Recovery will be independent of treatment and depends entirely on the establishment of collateral circulation or recanalization of the vessel.

If the patient survives long enough and the signs and symptoms persist over a prolonged period, this strongly suggests interference with the collateral flow, principally the azygos vein. If the underlying process is benign, surgery may be of benefit in the unusual, rare patient with a constricting band or scar.[4]

THERAPY

It has long been known that the symptoms and signs of venous obstruction will gradually subside spontaneously as the collateral circulation grows more efficient despite persistence of the block. Collins et al.[6] and Ray and Burch[7] have described the vascular changes following ligation of the inferior vena cava for suppurative thrombophlebitis of the pelvic veins. In all cases the edema, venous pressure and color changes tended to subside with time. The same findings have been noted by Roussak and Heppleston[8] in malignant disease occluding the inferior vena cava. In obstruction of the superior vena cava this improvement is even more likely to occur

spontaneously because of the effect of gravity on the return blood flow.

This series demonstrates that the syndrome may persist or progress despite intensive treatment. Improvement occurred in approximately one-third of the treated patients although the obstruction persisted. Our evidence indicates that a good clinical response in vena caval obstruction due to carcinoma and other infiltrative diseases depends upon the efficiency of the collateral circulation, chiefly the azygos vein. Generally, if the block involves or is below the azygos orifice improvement will be minimal.

When there is compression of the vein from without, as in aortic aneurysms, improvement may be obtained by removal of the mediastinal mass. However, even after the compressing agent is removed the obstruction may persist, indicating the important role of secondary thrombosis within the vessel. There appears to be no place for surgery in the therapy of the syndrome when it is produced by bronchogenic carcinoma.

In those less common conditions in which true external compression exists, excision of the mass or adhesions which compress or constrict the vessel is indicated. Under such circumstances immediate relief of the syndrome will depend upon the absence of a secondary thrombus. If a thrombus is present, recanalization may result in the gradual disappearance of the syndrome. Otherwise, improvement will depend entirely on the collateral circulation.

In rare cases of persistent superior vena cava syndrome due to azygos vein involvement from benign causes, it may be possible to duplicate Curtis's operation by reinserting the azygos vein below the point of obstruction.

While radiotherapy and chemotherapy do not relieve the primary block when it is due to an infiltrative tumor, they may still be of value in the treatment of the primary disease and in protecting the venous collaterals when the tumor is sensitive to these agents. Such improvement will usually be associated with radiologic evidence of reduction in size of the mediastinal mass.

Anticoagulants may be of value in preventing propagation of a thrombus and may thus help to preserve the collateral circulation. Specific therapeutic agents should be used when there is a definite etiology for the mediastinal process, such as tuberculosis.

No instance of superior vena cava obstruction due to malignant lymphoma was encountered in this series. Treatment with radiotherapy or chemotherapy is indicated in all cases of lymphoma but relief of the underlying vena caval block will depend upon the mechanism of the obstruction. If the vein is compressed by enlarged mediastinal lymph nodes, restoration of flow through the superior vena cava should occur unless a thrombus has formed. Details as to the mechanism of the block in patients with malignant lymphoma are difficult to obtain. Willis[9] reports one patient with Hodgkin's disease in whom the vein was infiltrated and occluded by the malignant process. Watson[10] cites a number of authorities (Ghon and Roman, Sternberg, Paltauf and Kundrat) who had similar experiences.

CONCLUSIONS

1. Twenty-one patients with superior vena cava obstruction were studied extensively during life and nineteen were followed to necropsy. The majority of these patients had infiltrative tumors, primarily bronchogenic carcinoma. Results of treatment in this group were disappointing. Of seventeen patients, ten failed to improve. In all seventeen patients the block persisted despite intensive treatment.

Persistence of vena caval block in bronchogenic carcinoma depends upon infiltration of the vascular wall. If compression of the superior vena cava by involved lymph nodes occurs, it is a rare finding.

2. There is no place for surgical therapy in the treatment of the syndrome when it is due to an infiltrative tumor. If radiotherapy or chemotherapy is used, it should be for its effect upon the primary tumor and secondarily to help preserve the collateral circulation. These forms of therapy will not relieve the obstruction when it is due to infiltration of the vein wall.

3. Excision of a mass producing compression, such as an aneurysm, gives relief of the syndrome unless secondary thrombosis has occurred.

4. It is obvious that the effectiveness of therapy in this syndrome depends entirely upon the underlying disease process. Even though the venous obstruction may persist, the natural tendency is for the symptoms and most of the signs slowly to be relieved spontaneously by the formation of collaterals.

Acknowledgment: We are indebted to Dr. Joseph Ziskind and Dr. Charles A. Jones for their interest and advice.

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A Critical Appraisal of the Concept of Bernheim's Syndrome*

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THE entity known as "Bernheim's syndrome" consists of symptoms and signs of pronounced right ventricular cardiac failure (venous hypertension, hepatomegaly and edema) appearing in the absence of dyspnea and orthopnea in cardiac lesions affecting primarily the left ventricle. This concept, introduced in France in 1910, postulates that marked hypertrophy of the left ventricle may deviate the cardiac septum to the right to the extent of producing a "stenosis" of the cavity of the right ventricle, which then leads to venous congestive phenomena. Such deviation of the cardiac septum encroaching upon the cavity of the right ventricle is thought to be demonstrable at autopsy. This clinicopathologic entity appears to have gained popularity within the past ten years as evidenced by several recent papers on the subject and by the inclusion of discussions of the Bernheim syndrome in most current textbooks.

Modern methods of study of the circulatory system permit direct assessment of various concepts created by the older clinicians. Many such concepts were fully confirmed, attesting the ingenuity and brilliance of the deductions of our medical forefathers. Others were discredited and abandoned to be replaced by new ones. Bernheim's syndrome represents a disturbance of the function of the right ventricle which should be amenable to direct scrutiny. Nowadays, a concept of this kind cannot rest on demonstration of morbid anatomic changes alone without a correlation with physiologic studies. It is proposed, therefore, to subject this concept to critical appraisal in the light of observations in a case of Bernheim's syndrome in which circulatory measurements were performed.

CASE REPORT

A sixty-two year old white man entered the hospital in January, 1954, because of swelling of ankles and legs and died six weeks later.

The patient was first admitted to the hospital in 1950 for the repair of a right inguinal hernia. At that time he had no cardiovascular symptoms and had no knowledge of hypertension, which was found on admission examination. Blood pressure averaged 210/120 during the hospital stay. No cardiac enlargement was found on physical examination and roentgenoscopy but the electrocardiogram showed the pattern of left ventricular hypertrophy. In late 1951 he had a seizure of severe epigastric pain associated with perspiration and syncope which was diagnosed as acute myocardial infarction and for which he was treated at home by a six-week period of rest in bed. He was able to return to work experiencing only mild weakness, until, several weeks later, in February, 1952, he suddenly developed exhaustion associated with some shortness of breath, and swelling of ankles, legs and scrotum. No orthopnea, paroxysmal or nocturnal dyspnea were experienced. He was readmitted to the hospital at which time his blood pressure was recorded as 180/120. Physical examination revealed that the patient lay comfortably flat in bed. The heart was enlarged to the left. A loud blowing apical systolic murmur was heard. Heart rate was 110 and the rhythm was regular. A few scattered rales were heard over both lungs. Markedly distended neck veins were noted when the patient was in the sitting position. Examination of the abdomen revealed hepatomegaly and ascites. Widespread edema involved the sacrum, genitalia and entire lower extremities. An

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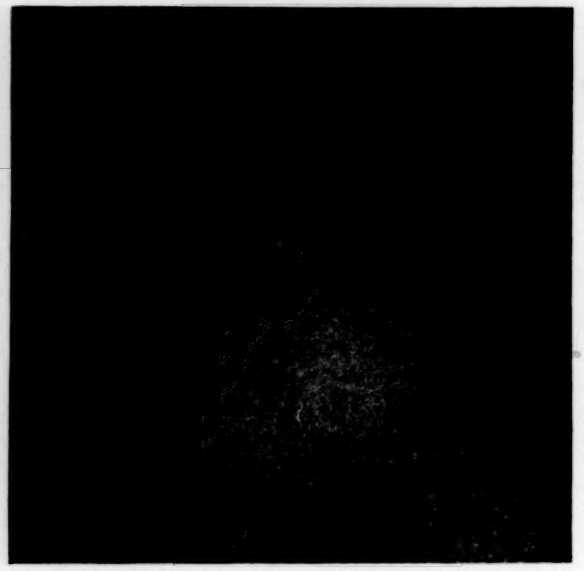

FIG. 1. Chest roentgenogram of the patient taken at the time of severe congestive cardiac failure, showing considerable cardiac enlargement, predominantly left ventricular, and virtual absence of pulmonary congestion and of pleural effusion.

electrocardiogram now showed, in addition to the features of left ventricular hypertrophy, evidence of posterior myocardial infarction.

The patient was treated with digitalis, low-sodium and low-caloric diet, diuretics and aminophyllin. He lost 34 pounds and was discharged completely free from symptoms.

In November, 1952, still asymptomatic, he reentered the hospital for removal of a parotid tumor. At that time hypertension and a cardiac murmur were recorded but no signs of cardiac failure were found.

Some time prior to his final hospital admission in January, 1954, his "low-salt" regimen was relaxed and he began to note recurrence of swelling of legs. He again experienced slight fatigue and dyspnea with exertion. As before, orthopnea and paroxysmal dyspnea were not present, nor was there a recurrence of chest pain or syncope.

His family history was remarkable in that both parents and an older brother died of heart disease, presumably associated with hypertension, between the ages of forty-five and sixty years. His past history was non-contributory with the exception of positive serologic tests for syphilis in 1945, for which he completed a course of antiluetic therapy consisting of penicillin and heavy metals.

Physical examination on the final admission revealed absence of respiratory distress or orthopnea. Blood pressure was recorded as 260/140. Advanced hypertensive retinopathy was noted. Very prominent venous distention was seen with pulsation. The heart was enlarged. There was an accentuation of the second sound in the aortic area. A moderately loud blowing apical systolic murmur was again heard and, in addition, there was a loud, long, high-pitched early diastolic murmur along the left sternal border. Hepatomegaly, ascites and anasarca were again present. The lungs were clear. Laboratory findings included a normal blood count. Urinalysis showed a trace of albumin and the specific gravity fixed at 1.010. Kahn and Kolmer tests were both positive. Chest roentgenogram showed marked cardiac enlargement but almost no evidence of pulmonary congestion. (Fig. 1.) The costophrenic angles were free from fluid. Electrocardiogram again showed evidence of previous posterior myocardial infarction with signs of left ventricular hypertrophy. Cardiac catheterization was performed shortly after admission, with the findings summarized in Table 1.

TABLE 1
SUMMARY OF FINDINGS ON CARDIAC CATHETERIZATION

Intracardiac pressures, mm. Hg	
Pulmonary artery "wedge"	48/30, mean 36
Pulmonary artery	88/36, mean 60
Right ventricle	85/17, mean 45
Right atrium	18
Arteriovenous oxygen difference at rest, vol. %	8.9
Resting cardiac output, L./min.	4.2

A therapeutic regimen of digitalis, bed rest, low-sodium diet and mercurial diuretics was successful in reducing the patient's weight by 26 pounds and eliminating all the signs of right ventricular failure. On March 2, 1954, the patient developed pain in the back, went into shock and coma, and died suddenly.

Necropsy Findings. The heart weighed 690 gm. The right ventricle measured 5 mm. and the left 20 mm. in thickness. The valves were within normal limits. The posterior portion of the left ventricle and the posterior septum showed marked scarring. An area of pale, grayish-brown muscle was found in the anterior portion of the left ventricular myocardium. The right coronary artery showed occlusion at its lumen approximately 1½ cm. distal to its origin, a subintimal hemorrhage producing part of the occlusion and a grayish-brown friable thrombus completely plugging the vessel. The left coronary

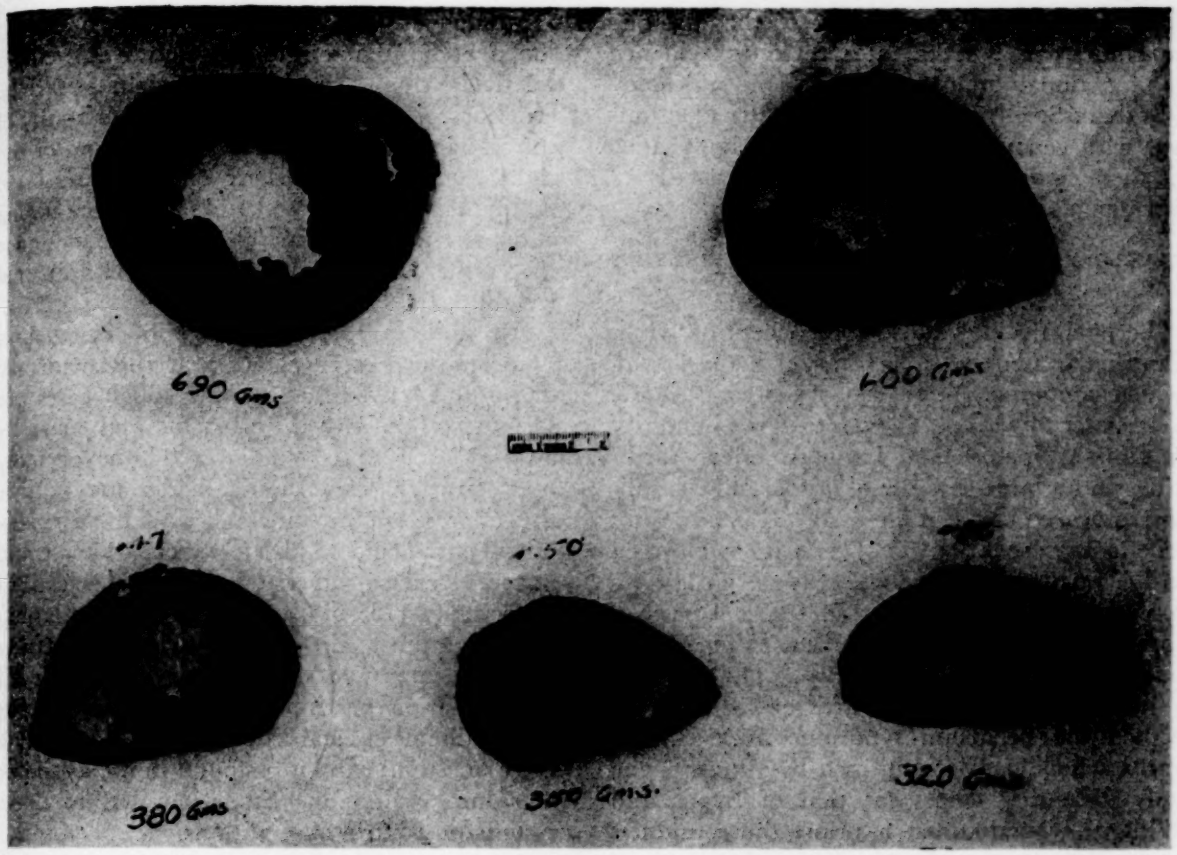

FIG. 2. Photograph of microtome slices of five hearts taken from transverse sections halfway between the apex and the base of the heart. These sections demonstrate the relationship of the two ventricular cavities, showing convexity of the cardiac septum "encroaching" upon the crescentic right ventricular cavity. Heart No. 44 represents the specimen from our case which presented clinical features of "Bernheim's syndrome"; No. 45, a heart from a patient with hypertensive disease and conventional cardiac failure; No. 47, 50 and 82 represent unselected hearts from individuals who had no clinical or pathologic evidence of cardiac disease.

artery showed an area of almost complete occlusion of its descending branch 2½ cm. from origin. A transverse cut through the heart halfway between the apex and the base showed the left ventricular cavity to be round and the right one crescentic, due to the convexity of the interventricular septum. (Fig. 2, No. 44.) The relationship of the two ventricular cavities appeared identical with other cases reported as instances of "Bernheim's syndrome."

The right lung weighed 500 gm. and the left 480 gm. Both contained clear air spaces with no evidence of congestion. The pleural spaces were free of fluid. No ascites was found. The liver weighed 2,000 gm. and showed the usual findings of passive congestion. The only other remarkable finding was a tumor nodule in the cortex of the right adrenal gland which measured 3 cm. in diameter and weighed 41 gm.

Comment. This case fulfills the most rigid criteria of the Bernheim syndrome: (1) The etiologic factors, hypertension and coronary disease, affected the left ventricle and led to its hypertrophy; (2) dyspnea, orthopnea and signs of pulmonary congestion were absent or negligible; (3) persistent, severe congestive failure of the "right ventricular" type was observed over a long period of time and (4) necropsy findings were those considered typical of the Bernheim syndrome, namely, a small crescentic cavity of the right ventricle due to the convexity of the interventricular septum, a large and congested liver and non-edematous lungs of normal weight.

A study of the circulatory dynamics performed at the height of clinically evident right ventricular failure with the patient lying comfortably flat revealed the following findings: (1) Severely elevated pulmonary "wedge" pressure, with a late systolic swing indicative of left ventricular failure with relative mitral regurgitation; (2) severe pulmonary hypertension with low dias-

tolic pressure which, in view of the diastolic murmur, can best be interpreted as evidence of functional pulmonary valve insufficiency (Graham-Steell) and (3) right ventricular failure with venous hypertension. The significance of these findings in relation to the concept of Bernheim's syndrome will be discussed later.

DEVELOPMENT OF THE CONCEPT OF BERNHEIM'S SYNDROME

Bernheim[1,2] introduced the concept of "right ventricular stenosis" in two articles, the first of which contained summaries of ten cases. Some years later this concept began to gain popularity in Italian, Spanish and Latin American medicine, and a large number of articles on the subject appeared between the years 1927 and 1940.[3] The first reference to the "Bernheim syndrome" in the English language was made in Fishberg's monograph on heart failure.[4] The first American case was reported in 1944[5] and since then several papers have been devoted to the subject.[6–11] With the exception of one article[12] all have accepted the Bernheim syndrome as a clinical entity which can be confirmed by autopsy. The only dissenting voice was that of Evans and White,[12] who doubted a priori the soundness of the concept of "right ventricular stenosis" and examined the clinical and pathologic data in cases with severe hypertrophy of the left ventricle. These authors produced a number of arguments against the existence of such an entity. At the present time the Bernheim syndrome appears to be well enough known to deserve comment in most current textbooks. It has been accepted by some authors,[13–15] considered an unproven controversial issue by others[16,17] and rejected by still others.[18,19] In recent books[20,20a] the Bernheim syndrome is discussed at length. Furthermore, one finds references to this syndrome in informal discussions and presentation of cases.[21]

It is thus seen that the concept of Bernheim's syndrome, in spite of some scepticism, has found fairly wide acceptance among clinicians and pathologists. It appears, however, to have been ignored by the physiologists as no references to it can be found in writings concerning physiopathology of cardiac failure.

PATHOLOGY OF BERNHEIM'S SYNDROME

The pathologic criteria postulated by the various proponents of the Bernheim syndrome consists of marked hypertrophy of the left ventricle with the septum assuming a curved shape and bulging into the right ventricle; a relatively small cavity of the right ventricle, crescentic in shape; slight or no hypertrophy of the right ventricular wall and dilatation of the right atrium. Evans and White[12] postulated additional criteria: absence of pulmonary edema and presence of hepatic congestion as evidence by the increased weight of the liver and normal weight of the lungs.

All authors reporting cases of Bernheim's syndrome accept as a fact that this syndrome constitutes an anatomic entity. Such cases are said to be "diagnosed during life and *proven* by autopsy" or even "discovered unexpectedly by necropsy."[6] The casual reader may gather the impression that one deals with an undisputed pathologic condition. Such a view could not survive a critical scrutiny. A critic is justified in asking two questions: What is the relationship of the septum to the right ventricular cavity in normal hearts, and what is it in cases with left ventricular hypertrophy which followed the conventional clinical course? The answers to these questions cannot be found in the available literature, as no one has attempted to make systematic control observations.

Apparently Bernheim's drawing[1] presenting a straight cardiac septum with equal cavities of the two ventricles in normal hearts and a deviated septum with a large left and a small right cavity as an example of his "syndrome" has been accepted as an axiom. Yet this drawing appears to be a distorted diagram not representing the true condition, for textbooks of anatomy state that the cardiac septum is curved and bulges into the right ventricular cavity. The left ventricular cavity normally has a round shape and the right ventricular cavity is crescentic. This can best be demonstrated by a transverse cut through the heart at a distance halfway between the apex and the base, which is the section through the heart used as a means of demonstrating the "Bernheim syndrome." Since such a cut through the heart is not part of the routine examination of the heart at necropsy, the average observer is unfamiliar with this appearance of the heart. Figure 2 shows a photograph of microtome slices of three normal hearts showing the "encroachment" of the septum into the right ventricular cavity. The upper two hearts represent those with left ventricular hypertrophy, namely, that of our patient exhibiting clinical features of the Bernheim syndrome and the heart of another

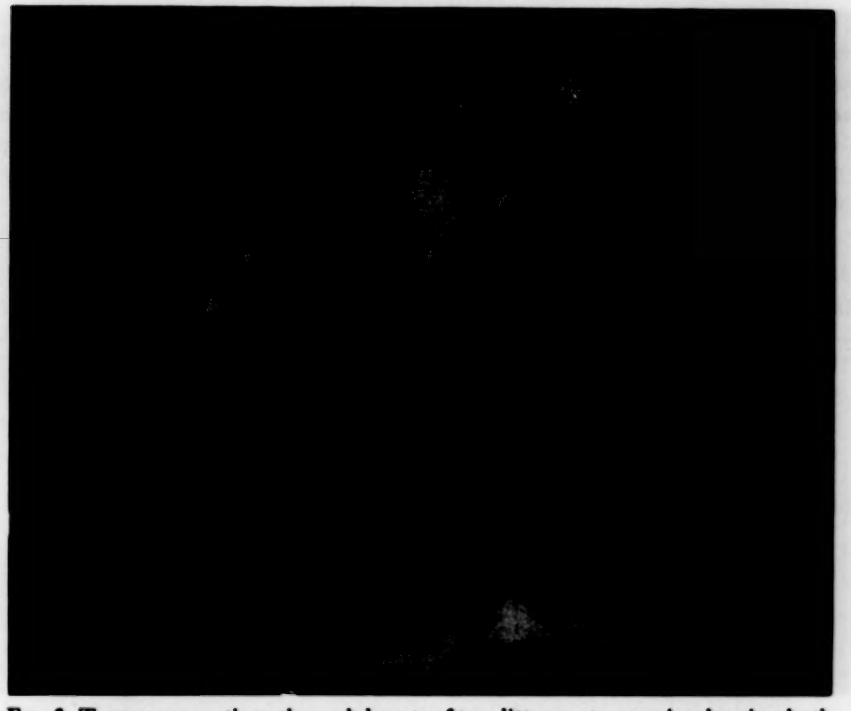

FIG. 3. Transverse sections through hearts of two litter mate puppies showing both the apical and basal portions of the cut. The upper heart is from the puppy with left ventricular hypertrophy due to experimental aortic stenosis,[22] the lower one being the control normal heart.

hypertensive patient who followed a conventional clinical course. One can also recall that Atlas and associates[9] reported a case of Bernheim's syndrome and compared the anatomic findings in it with four other cases with left ventricular hypertrophy and a conventional clinical course. The Bernheim case and the four other cases showed identical weights and measurements. The authors interpreted this by stating that weight and measurements "bear no relationship to the encroachment by the septum." Yet the two "control" hearts illustrated in their paper show an unmistakably convex septum and differ from the "Bernheim" heart only in somewhat more pronounced dilatation of the right ventricle. Finally, one can best illustrate the fact that the cardiac septum physiologically "encroaches" on the right ventricular cavity by showing such a relationship in a dog's heart, in which the contrast in musculature of the two ventricles is more marked than in the human heart. Figure 3 shows the hearts of litter mate puppies, one of which developed left ventricular hypertrophy as a result of experimental aortic stenosis.[22] It can be seen that both the normal and hypertrophied hearts show more "right ventricular stenosis" than any of the reported cases of Bernheim's syndrome.

It is clear that "encroachment" of the cardiac septum on the cavity of the right ventricle appears to be a normal phenomenon, or may be an accentuation of normal conditions by left ventricular hypertrophy. It should also be pointed out that other pathologic criteria of Bernheim's syndrome rest on equally shaky grounds. The width of the crescentic right ventricular cavity and the thickness of the right ventricular wall at the autopsy table need not reflect the situation during life. The degree of dilatation of a cardiac ventricle postmortem depends on many extraneous factors, such as the terminal illness, the mode of death, action of various drugs and the presence or absence of rigor mortis, so that any conclusion as to the significance of these findings is extremely hazardous.

Finally it should be pointed out that the theoretic criteria for the pathologic diagnosis of the Bernheim syndrome have not been fulfilled by the majority of cases, as can be demonstrated by tabulating all the cases reported in the English language. (Table II.)

On the basis of the foregoing considerations

one is justified in concluding that the necropsy findings alleged to "prove" the existence of Bernheim's syndrome are based on misconceptions of the normal relationship and are therefore unacceptable.

It should be mentioned in passing that there are a few reported cases of encroachment of the cavity of the right ventricle by structures other than the hypertrophied left ventricular septum: Aneurysm of the infarcted ventricular septum and cardiac tumors. Such cases have been considered by some to be variants of the Bernheim syndrome.[23,24]

TABLE II

PRINCIPAL CLINICAL AND PATHOLOGIC CRITERIA OF BERNHEIM'S SYNDROME AND THEIR FULFILLMENT BY CASES REPORTED IN THE ENGLISH AND AMERICAN LITERATURE

Authors	Clinical Criteria						Pathologic Criteria				
	Absence of Dyspnea *	Absence of Orthopnea	Absence of Pulmonary Edema	Absence of Pulmonary Rales	Absence of Pulmonary Congestion in Roentgenogram	Rt. Ventricular Failure	Weight of Heart	Small Rt. Ventricular Cavity	Rt. Ventricular Wall Less Than 5 mm. Thick	Lung Weight Less Than 1,000 gm.	Liver Weight More Than 1,700 gm.
Glushien[5]	−	−	+	−		+	980	+	+	−	+
Russek[6]	+	+	+	+	+	+	710	−	−		−
Russek[6]	±	+	+	±	+	+	725	+	−		+
Russek[6]	−	+	+	+		+	800	−			−
East and Bain[7]	+	+	+		±	+	720			+	
East and Bain[7]	−	+	+	−	−	+	600	+	−	+	
East and Bain[7]	−	−				+	810	−	+	+	−
East and Bain[7]	+	+	+			+	540			+	
Russek[8]	−	+	+			+	750	+	+	−	+
Atlas[9]	±	+	+	−	−	+	700	−	−	+	
Wilson[10]	−	+	+	+	+	+		+	+	−	−
Cordeiro[11]	+		−	+	+	+	775	±			
Our case	±	+	+	+	+	+	690	+	+	+	+

* Table is arranged in such a manner that + signifies fulfillment of the criterion; ± borderline or questionable and − lack of fulfillment. Blank spaces indicate that information is not given.

PATHOPHYSIOLOGY OF BERNHEIM'S SYNDROME

The contention that the normal heart shows a round left ventricular cavity and a crescentic right ventricular cavity, as seen in the transverse section through the mid-portion of the heart at necropsy (Fig. 2), can be supported by observations made during life. Rushmer and Thal[25] studied the mechanics of ventricular contraction in the dog by means of cinefluorography and concluded that "the right ventricular area is bounded by the concave surface of the free wall and the convex sur-

face of the septum, producing a semilunar configuration in cross section." Furthermore, Rushmer et al.[26] presented evidence that contraction of the right ventricle involves the shortening of the free wall and drawing of the tricuspid ring toward the apex of the heart. This mechanism is thought to explain the fact that mass destruction of the right ventricular musculature does not lead to right ventricular failure. It appears, therefore, that the crescentic shape of the right ventricular cavity enhances, rather than hinders, the proper functioning of the right ventricle. If septal hypertrophy were to lead to an exaggerated convexity and bulging into the right ventricular cavity, there is no reason to suppose that the right ventricle would not maintain its working blood capacity by dilating its free wall, which apparently plays only a lesser role in right ventricular pumping action. Acute dilatation of the right ventricle can be demonstrated in the dog by producing artificial resistance by graded constriction of the pulmonary artery.[27] In such experiments higher degrees of constriction produce very considerable dilatation of the basal part of the right ventricle, yet the dilated right ventricle works most efficiently by elevating its systolic pressure fourfold and maintaining an almost normal end-diastolic pressure.

Thus the concept of the hypertrophied septum encroaching on the cavity of the right ventricle and interfering with its function is thought to be not only highly improbable but also actually inconsistent with present day concepts of cardiac function. It seems equally doubtful that aneurysm of the septum could produce interference with right ventricular function. The circulatory effect of invasive cardiac tumors cannot be properly analyzed because of the multiplicity of factors involved. It is altogether unlikely that any structural change within the heart itself could ever have a restrictive influence upon diastolic filling in a manner similar to constrictive pericarditis. However, if Bernheim's concept of right ventricular stenosis were correct, the dynamic changes would have to be analogous to those found in constrictive pericarditis affecting primarily the right heart.[28] Both in right-sided constrictive pericarditis and in a hypothetic case of true Bernheim's syndrome one would expect to find no dynamic changes in the left side of the heart and in the pulmonary circulation. Pulmonary "wedge" pressures and pulmonary arterial pressures should be normal. With no increase in resistance within the pulmonary circuit the systolic pressure in the right ventricle should be normal, but the diastolic pressure should be elevated in proportion to the degree of interference with diastolic filling. Right atrial and peripheral venous pressure should be increased accordingly. Comparing these hypothetic findings with those actually recorded in our case of clinically and pathologically typical Bernheim syndrome it is obvious that in our case an entirely different circulatory derangement took place. Severe failure of the left ventricle and marked pulmonary hypertension were recorded. Furthermore, both the cardiac murmurs and the dynamic tracings suggest strongly that functional insufficiency of at least two valves (mitral and pulmonary) was present, although both were found unaltered anatomically. Functional insufficiency due to dilatation of the mitral ring and pulmonary orifice occurs usually with especially severe and long-standing dynamic alterations. It is evident, therefore, that in this case the conventional chain of events in a hypertensive subject with cardiac failure occurred: left ventricular failure, pulmonary hypertension and right ventricular failure.

PHYSIOLOGIC BASIS FOR THE SYMPTOMATOLOGY OF BERNHEIM'S SYNDROME

The traditional concept of left- and right-sided cardiac failure has not only survived criticism but has established itself more firmly than ever in the light of recent hemodynamic studies. The apparent discrepancy between an isolated left ventricular lesion and the clinical picture of pure right ventricular failure prompted some clinicians to accept Bernheim's concept of right ventricular stenosis bypassing the pulmonary circulatory difficulty. Yet the discrepancy may be more apparent than real. While in the average case of cardiac failure due to left-sided heart disease isolated left ventricular failure may or may not be present, signs of left ventricular failure persist when right ventricular failure develops. However, it is a well known clinical fact that patients who develop severe right ventricular failure occasionally lose signs and symptoms of pulmonary congestion, including dyspnea and orthopnea. There is no question, in such instances, as to right-sided failure being secondary to failure of the left ventricle. If one therefore recognizes that chronic cardiac failure may proceed through three stages: pure

left ventricular failure, combined left and right heart failure and pure right ventricular failure, then the Bernheim syndrome may simply represent those cases in which the first and second stages are clinically inconspicuous. The reason for the absence of signs and symptoms of pulmonary congestion is not yet known. It is noted, however, that dyspnea and signs of pulmonary congestion appear to be related, at least in part, to the uneven distribution of the blood volume by "trapping" of blood in the pulmonary circuit due to temporary inequality of the output of the two ventricles, when the left ventricle fails and the right maintains good function.

Severe right ventricular failure, when associated with tricuspid insufficiency, is thought to "decongest" the lungs by redistributing the increased blood volume more evenly. If a mechanism were operating which could minimize the accumulation of blood in the pulmonary circuit, combined heart failure would manifest itself clinically as pure right ventricular failure, producing the symptomatology of Bernheim's syndrome. Such a mechanism could conceivably be related to active pulmonary arteriolar constriction. There is some evidence, at least in mitral stenosis,[29] to suggest that patients with severe pulmonary hypertension are significantly less dyspneic than those with milder pulmonary hypertension. It has also been suggested[30] that in some cases of aortic valvular disease increased pulmonary resistance may be evident before significant left ventricular failure is apparent. One could thus visualize instances in which early appearance of increased pulmonary resistance developing with incipient left ventricular failure could on one hand minimize pulmonary congestion, and on the other accelerate and aggravate right ventricular failure, thus bringing about the syndrome under discussion.

It should be mentioned that differential circulation time test (arm-to-lung and arm-to-tongue) has been used by some as confirmatory evidence of the Bernheim syndrome. This crude and unreliable test depends upon many factors other than cardiac failure and is entirely unsuitable for any quantitative differentiation of the type of cardiac failure.

DISCUSSION

In the foregoing presentation various clinical, pathologic and physiologic observations were cited supporting the view that Bernheim's syndrome is not an acceptable clinical or pathologic entity. One can further point out various inconsistencies in the development of the concept. To begin with, in quoting the original article of Bernheim[1] it has been generally overlooked or ignored that none of the ten cases reported in it represents the clinical picture of Bernheim's syndrome: five patients were never in failure at all, having died of non-cardiac causes, and the other five presented varying degrees of chronic dyspnea. Apparently Bernheim collected a series of cases at the autopsy table in which a hypertrophied left ventricle "stenosed" the cavity of the right ventricle, and speculated upon what the clinical picture should be rather than observing the actual course.

Bernheim's syndrome appears to be rare although one group[31] claims to have observed personally fifteen cases. On the other hand, a survey of 2,000 consecutive autopsies in a general hospital[12] failed to find a single case to fulfill all the criteria. In this connection, the laxity in fulfilling the criteria in the reported cases of Bernheim's syndrome should be pointed out. Dyspnea has been found in many of the cases. In anticipation of criticism, some authors[8–10] suggested that its presence does not rule out the Bernheim syndrome because left ventricular failure and right ventricular stenosis may coexist. Other criteria also remained unfulfilled in some cases, as seen in Table II, in which other examples cited are compared with our case.

Our case is not submitted solely as evidence against the Bernheim concept of right ventricular failure, for it is fully realized that no single instance, even if "ideal," can prove or disprove the existence of a syndrome. Rather, the case serves to corroborate clinicopathologic and experimental observations which are believed to demonstrate that the concept of Bernheim's syndrome is clinically, physiologically and anatomically unsound. The concept of interference with right ventricular function by the "deviated" septum is in conflict with the fundamentals of present day cardiac physiology.

The question as to why some patients show prominent systemic congestive phenomena without demonstrating signs of pulmonary congestion remains unanswered and will have to await further studies on the pathogenesis of dyspnea and pulmonary congestion.

Several years ago Evans and White made an

unsuccessful plea for abandonment of the concept of Bernheim's syndrome. It is to be hoped that this term eventually will be dropped from current terminology.

SUMMARY AND CONCLUSIONS

1. A case is reported of a man with hypertensive and coronary heart disease who suffered from long-standing systemic congestive cardiac failure without ever exhibiting significant dyspnea, orthopnea and pulmonary congestion. At necropsy the cardiac septum was found to be deviated to the right, "stenosing" the cavity of the right ventricle. This case is shown to fulfill the clinical and pathologic criteria of Bernheim's syndrome, and yet hemodynamic studies revealed the following conventional findings: left ventricular failure, pulmonary hypertension and right ventricular failure.

2. Evidence is presented that the pathologic substrate of the Bernheim syndrome is based upon a misconception, for the cardiac septum normally is deviated to the right, "encroaching" upon the crescentic cavity of the right ventricle, and this relationship appears exaggerated in any heart with a hypertrophied left ventricle, regardless of clinical course.

3. Experimental observations are cited which suggest that the Bernheim concept moreover is inconsistent with present day knowledge of the mechanics of ventricular function.

4. Cases reported as instances of the Bernheim syndrome apparently represent examples of cardiac failure with conventional dynamic changes, in which dyspnea, orthopnea and pulmonary congestive phenomena are inconspicuous. Possible reasons for the absence of dyspnea are discussed.

5. The term, Bernheim syndrome, should now be abandoned.

Acknowledgment: The authors are indebted to Dr. John B. Frerichs, Chief of Pathological Anatomy, and to members of his staff for providing the pathologic data and the special sections of the hearts.

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Adams-Stokes Syndrome*

The Treatment of Ventricular Asystole, Ventricular Tachycardia and Ventricular Fibrillation Associated with Complete Heart Block

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THE syndrome of syncope with slow pulse rate was first observed and described accurately by Morgagni[1] in 1767. Adams[2] observed it in 1827 and Stokes[3] published four case reports in 1846. Since that time syncopal attacks associated with heart block have been known as the Adams-Stokes or Morgagni-Adams-Stokes syndrome.

Until recently it was generally believed that these attacks occur only when the ventricular diastole is sufficiently prolonged to cause cerebral ischemia. In the third edition (1940) of Nomenclature and Criteria for Diagnosis of Diseases of the Heart[4] the Adams-Stokes syndrome is defined as follows: "This term is applied to attacks characterized by unconsciousness, often accompanied by muscular twitchings and even convulsions. These attacks occur in patients with auriculoventricular block when the ventricular diastole is sufficiently prolonged to result in a severe grade of cerebral ischemia." However, in the 1947 edition an important correction recognized another mechanism responsible for Adams-Stokes seizures, namely, transient ventricular fibrillation.

As early as 1927 Wenckebach and Winterberg[5] mentioned Adams-Stokes attacks due to ventricular tachycardia and fibrillation. Although there was complete A-V dissociation in these cases, they believed that the attacks were the result of a series of very rapid and irregular ventricular systoles (ventricular tachycardia and fibrillation) resulting in cerebral ischemia. In 1941 Parkinson, Papp and Evans,[6] after analysis of sixty-four cases of Adams-Stokes syndrome in which electrocardiographic studies were made, found that ventricular tachycardia or fibrillation was the mechanism for the attacks in almost half the cases. They defined the Adams-Stokes syndrome as "that condition which is seen in patients with complete heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these."

Groedel and Kisch[7] also drew attention to transient ventricular tachycardia as a possible second mechanism for Adams-Stokes seizures. Fishberg[8] concisely summarized the end-result of all possible cardiac conditions in question by defining the Adams-Stokes syndrome as an example of paroxysmal cerebral ischemia due to diminution of the output of the left ventricle. De Boer[9] suggested an even broader concept. He included under the term Adams-Stokes syndrome "every disturbance of the action of the heart that begins and ends abruptly and causes such interruption of the circulation that more or less complete cerebral ischemia results."

Schwartz, Orloff and Fox[10] emphasized that it may be possible to predict clinically the imminent onset of ventricular fibrillation in the course of complete A-V block. The patient may note an increase in the heart rate prior to a syncopal attack and auscultation may reveal frequent interruptions of the slow basic rhythm by short runs of more rapid and weaker beats. These rhythmic disturbances may coincide with pallor or a sensation of lightheadedness.

Electrocardiograms taken during such premonitory periods may show prefibrillatory phenomena which should make one suspect impending ventricular fibrillation. These prefibrillatory phenomena have been noted[10] to have the following characteristics: (1) lability of the basic ventricular rate; (2) appearance of premature ventricular beats, at first singly and then in groups of varying length; (3) appearance

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of bizarre and deformed ventricular complexes; (4) finally, the appearance of definite fibrillatory waves.

The importance of differentiating these different cardiac mechanisms, namely, ventricular asystole and ventricular fibrillation, is stressed because rational therapy and prevention of Adams-Stokes attacks is based on such knowledge. When the mechanism of syncope is ventricular standstill, epinephrine is the drug of choice and may be life-saving. However, this drug, in addition to acting upon and stimulating the basic ventricular pacemaker, may set up lower ectopic foci within the ventricles which may initiate runs of multifocal ectopic beats and even ventricular fibrillation. This may occur in certain hypersensitive individuals even when the dose of the drug administered is not unusually large. In such cases epinephrine must be used with the utmost caution, under electrocardiographic control. Moreover, when the mechanism for the attack is known to be ventricular fibrillation, administration of epinephrine is ineffective and can be dangerous.

On the other hand, one would expect in theory at least that anti-arrhythmic drugs such as quinidine and procaine amide would be effective in preventing or abolishing ventricular tachycardia or fibrillation, and the use of these drugs often has been recommended in such cases. In the past few years, however, numerous authors[11–24] have reported undesirable and dangerous disturbances in cardiac rhythm resulting from the use of quinidine and procaine amide in the presence of heart block and bundle branch block.

Kerr and Bender[11] observed attacks of ventricular fibrillation in a patient with complete heart block during a course of quinidine therapy. Schwartz and Jezer[12] administered quinine and quinidine to two patients with complete heart block and found that both drugs, given intravenously in small doses, consistently induced a pre-fibrillatory mechanism or transient periods of ventricular fibrillation. Robertson and Matthews[13] treated a patient with Adams-Stokes syndrome due to paroxysmal ventricular fibrillation with quinidine sulfate administered orally and intravenously. They noted that the number of seizures did not decrease but became more frequent. The patient died during an attack of ventricular fibrillation as confirmed by an electrocardiogram recorded during the terminal episode. Fahr[17] pointed out that in a patient with disease of the bundle tissues quinidine, by increasing the existing block, may incite and perpetuate ventricular fibrillation. According to Scherf and Boyd[18] quinidine should not be given to a patient with heart block because it may precipitate ventricular fibrillation. Di Palma and Schults[19] in one year collected ten cases of severe quinidine myocardial toxicity occurring when this drug was administered in the presence of conduction defects. They concluded that quinidine should not be used when complete heart block, bundle branch block or intraventricular conduction defect are present.

The first reports of clinical trials with procaine amide (pronestyl®) in ventricular arrhythmias showed this drug to be very effective. More recently, however, several reports[20–24] have called attention to a serious effect of intravenous administration of procaine amide, namely, precipitation of ventricular arrest or, paradoxically, even of ventricular fibrillation. This applies particularly to cases in which there was damage in the A-V conduction system. Wedd and co-workers[20] found that this drug has a marked depressant action on the region of the junctional tissues and they warned that its use in the presence of diseased junctional tissues might be dangerous. Schwartz and associates[21] studied the effects of procaine amide in three patients with transient ventricular fibrillation during established A-V dissociation. They found that the drug depressed impulses formation in the A-V node as well as conduction in the junctional tissues and ventricles, and therefore favors the development of ectopic beats in the ventricles, leading to ventricular tachycardia and finally to fibrillation. They warned that the use of procaine amide is contraindicated in patients with transient ventricular fibrillation associated with A-V dissociation.

Miller, Nathanson and Griffith[22] reported results in four patients with complete heart block given procaine amide intravenously while the electrocardiogram was recorded. A definite reduction in ventricular rate was noted in all cases. In two patients frequent multifocal ventricular fibrillation was followed by a period of ventricular standstill. The fourth patient had frequent attacks of ventricular fibrillation. Procaine amide had no effect on the attacks and did not eliminate short paroxysms of ventricular tachycardia which occurred between major attacks. These observations indicate

that administration of this drug in complete heart block is ineffective and may be hazardous. This is in contrast to the well known action of the drug in abolishing ventricular premature beats and ventricular tachycardia in the absence of heart block.

Wegria and his associates,[23] after extensive studies on the use of procaine hydrochloride in cardiac resuscitation from ventricular fibrillation in dogs, determined that procaine slows the rate of the fibrillatory process and may even stop fibrillation. However, a dose of this drug sufficient to stop fibrillation depressed the rhythmicity of the heart to such an extent that after fibrillation was terminated a long period of ventricular standstill ensued. This would make its use dangerous in the presence of heart block.

In a more recent report Epstein[24] also observed ventricular arrest following very slow intravenous injection of procaine amide in three cases of ventricular tachycardia. Two of his patients had septal infarction probably affecting the junctional tissues. He, too, concluded that intravenous procaine amide is contraindicated in septal infarction, in bundle branch block and in the presence of any degree of A-V block.

To date, no defibrillatory drug has been discovered which is safe in the sense that all fibrillatory activity can be abolished while still leaving the myocardium with an effective pacemaker and the ability to respond to the pacemaker stimulus.[25] Di Palma and Schults[19] state that an antifibrillatory drug should "lengthen the refractory period without producing a supranormal state. It should prevent or eradicate local blocks and restore or maintain the normal propensity of the myocardium to act as a whole. It should not have undue vagal stimulating properties and it should not unduly depress the contractility of the myocardium or slow conduction." Unfortunately, the deleterious effects of quinidine and procaine amide on the myocardium and junctional tissues may outweigh the beneficial effects on the fibrillatory process, and they may thus be unsuccessful or harmful as therapeutic agents.

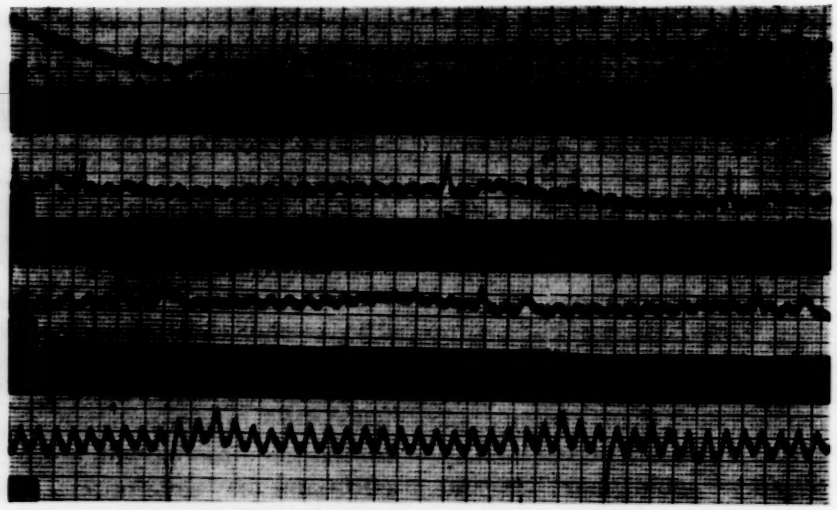
A drug recently introduced for the treatment and prevention of cardiac arrest, especially that associated with heart block, is an epinephrine-like compound, isopropyl nor-epinephrine (isuprel®). Pharmacological studies[26,27] show that isopropyl nor-epinephrine has a potent effect on the rhythmicity of the heart. While epinephrine stimulates both the higher and lower cardiac rhythmic centers, thus predisposing the ventricles to fibrillation, isuprel acts predominantly on the higher centers and nodal tissues without exciting lower ventricular foci. When the mechanism precipitating syncopal attacks in the Adams-Stokes syndrome is difficult to determine, or when both mechanisms, i.e., ventricular standstill and fibrillation, are present alternately in one patient, isuprel is the drug of choice. When the causal mechanism is ventricular standstill, isuprel, by stimulating a single active focus in the ventricle will be effective. When the causal mechanism is ventricular fibrillation, isuprel will exert no unfavorable effect and may even prevent further paroxysms of fibrillation, thus is to be preferred to epinephrine, quinidine or procaine amide.

The various problems in treatment and selection of the drug of choice will be illustrated in four cases of heart block accompanied by Adams-Stokes seizures. A-V block was associated with atrial flutter in three of these four cases. This combination is very rare. Jolly and Ritchie[28] in 1911 reported the first case of this combination of arrhythmias. Jourdonais and Mosenthal[29] surveyed and collected all cases reported up to 1937 and these totaled only twenty-nine. Since 1937 there have been about forty additional reported cases. The rarity of this combination is further illustrated by the fact that Willius[30] encountered it only once in 40,000 electrocardiograms, and Smith and Smith[31] noted it only three times in 25,000 consecutive electrocardiograms. This subject has been recently reviewed by Korst and Wasserburger.[32]

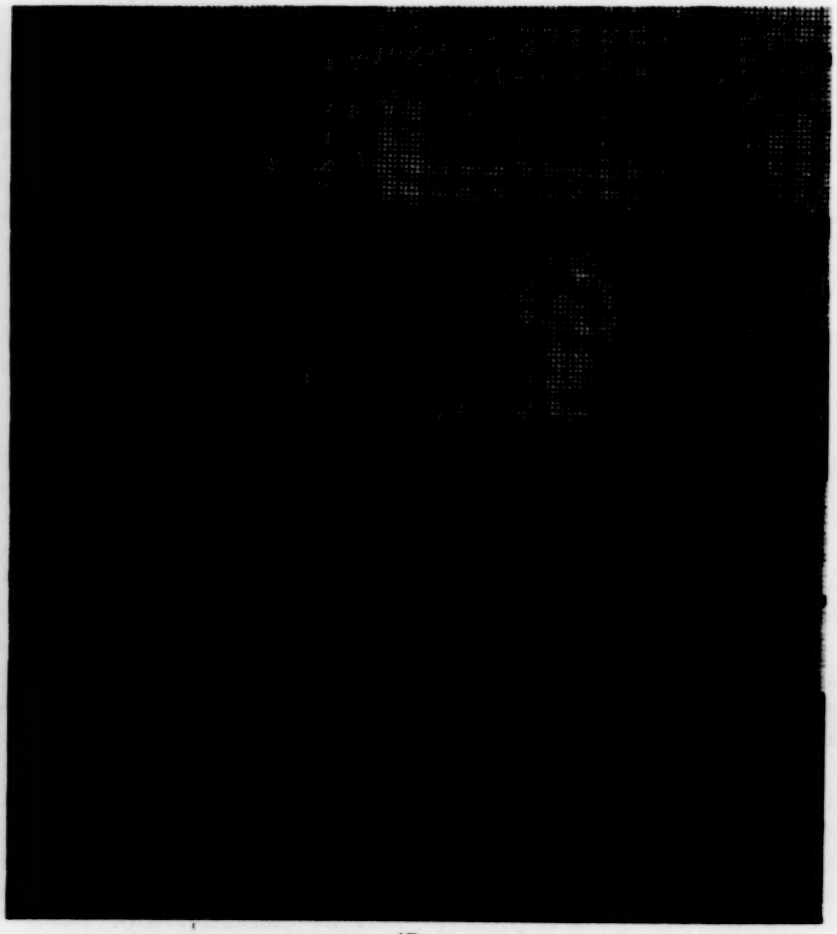
The practical application of isuprel will be described in two cases. In one case, in which ventricular fibrillation was responsible for the Adams-Stokes syndrome, quinidine and later procaine amide were administered without effect or possibly with deleterious effect. However, following administration of isuprel in repeated doses the periods of ventricular tachycardia and fibrillation ceased and the heart rhythm reverted to partial A-V block and later to normal sinus rhythm.

CASE REPORTS

CASE 1. B. K., a fifty-seven year old white male, was first seen in 1937 at which time he reported the occurrence of dizzy spells. Physical examination and x-ray studies revealed the presence of mitral stenosis without cardiac



1A



1B

FIG. 1. Case 1. A, record taken in 1947 during recurrent Stokes-Adams episodes, showing atrial flutter-fibrillation with A-V dissociation and long periods of ventricular asystole. B, record taken February, 1953 still shows atrial flutter-fibrillation with complete A-V dissociation. The ventricular rate is now regular, averaging 40 per minute. There is an occasional ventricular extrasystole. No ventricular asystole was observed.

enlargement. When next seen in 1946 he complained of frequent dizziness and fainting spells. Electrocardiograms taken on this occasion showed atrial flutter with complete A-V dissociation. The ventricular rate was 40 beats per minute. When the patient complained of faintness, the electrocardiogram showed a very slow idioventricular rate of 15 to 20 per minute with frequent premature beats. (Fig. 1A.) The average ventricular rate, therefore, ranged between 24 and 30 per minute.

One year later the patient reported that he had been hospitalized for a long time because of frequent syncopal attacks. Electrocardiograms showed atrial flutter-fibrillation with complete A-V dissociation and very slow ventricular rate. At the hospital the patient had been treated with a variety of drugs including epinephrine, ephedrine, barium chloride and testosterone.

When last seen approximately six years later the patient was leading a normal life. The syncopal attacks had become infrequent and the only medication taken was coramine,® 1 cc. orally, three times daily. The electrocardiogram (Fig. 1B) still showed atrial flutter-fibrillation with complete A-V block but the ventricular rate was 40 per minute and regular, except for an occasional ventricular premature beat.

Case II. M. W., a forty-eight year old white male, entered The Mount Sinai Hospital January 30, 1946, because of recurrent attacks of unconsciousness for the preceding two weeks. He had had an attack suggesting acute coronary occlusion six years before, followed by symptoms of coronary insufficiency on effort. A slow fixed pulse rate of 40 per minute had been noted for three years.

Following an operation for anal fissure four weeks before admission he began to have attacks of substernal pain, crushing in character and radiating to the precordium and into the left shoulder. In the few days prior to admission, the precordial pain became more severe and he had increasingly frequent attacks of unconsciousness. These started with slowing of the pulse rate, a "black out" of vision and then complete unconsciousness and twitching of the extremities. During the attacks the pulse rate slowed to 12 to 24 per minute.

The electrocardiogram on admission (Fig. 2A) showed complete A-V dissociation. The auricular rate was irregular due to frequent auricular premature impulses, and ranged from 80 to 100 per minute. The idioventricular rhythm was also irregular, ranging from 23 to 33 per minute, and was interrupted by frequent ectopic ventricular beats. The patient was treated with oxygen and injections of epinephrine in oil (1:500) three times daily, aqueous

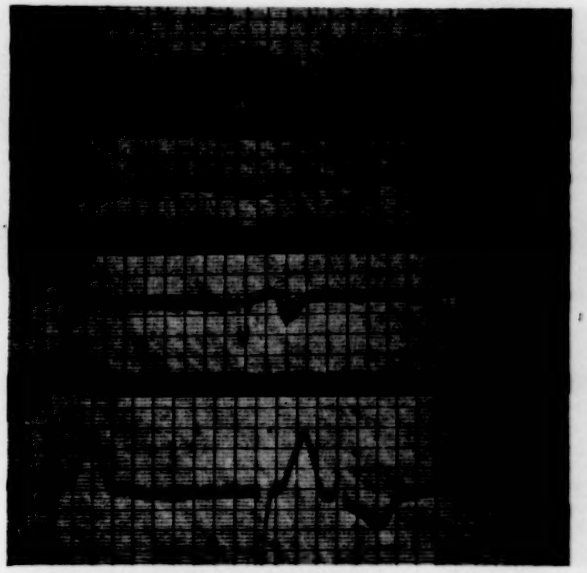


Fig. 2A. Case II. January 31, 1946. The record shows complete A-V dissociation with frequent ventricular ectopic beats. The ventricular rate ranges from 22 to 33 per minute.

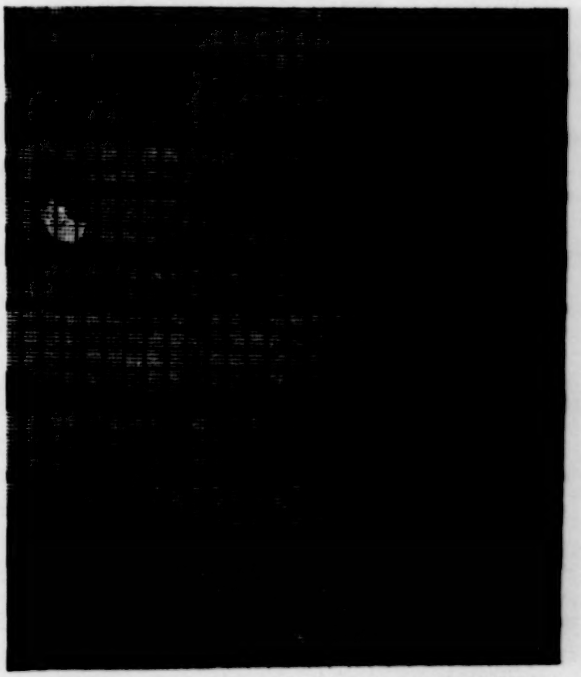
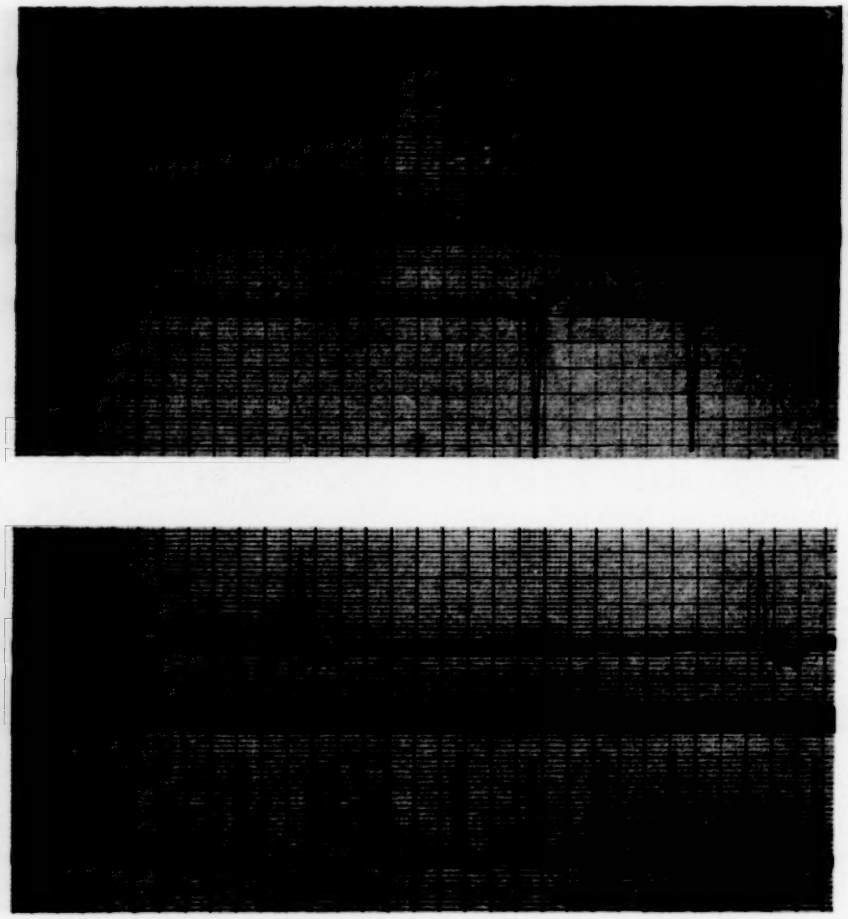


Fig. 2B. Case II. February 1, 1946. Complete A-V dissociation with a very slow ventricular rate is still present (12 to 28 per minute). Atrial flutter-fibrillation is also present. The Adams-Stokes attacks continued despite large doses of epinephrine.



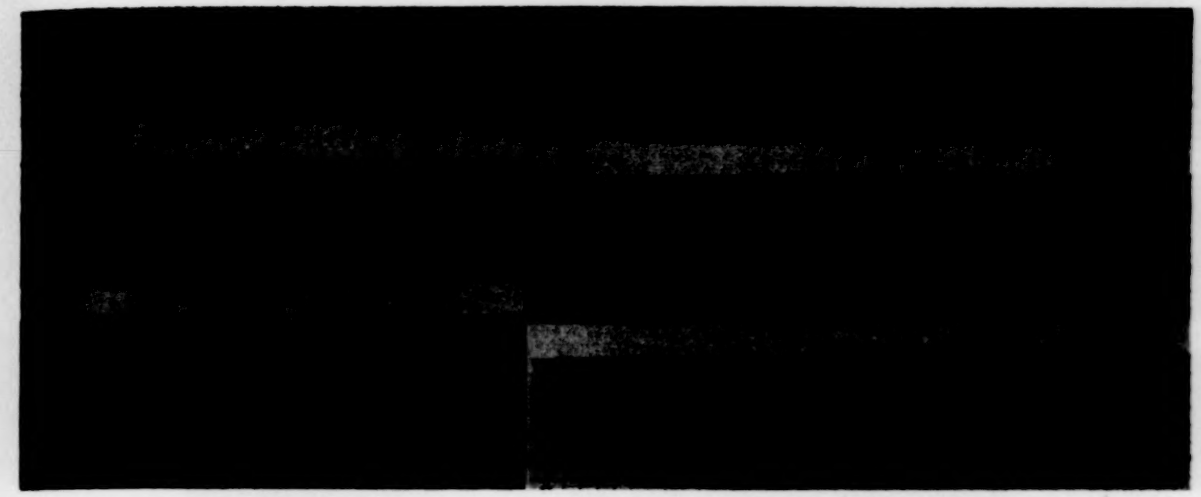
3A

FIG. 3A. Case III. January 6, 1953. Continuous strips of leads V_2 and V_5 taken during a syncopal attack show a peculiar atrial arrhythmia probably due to atrial flutter. The atrial rate varies from 110 to 300 per minute. There is partial A-V dissociation with periods of ventricular asystole lasting several seconds.

epinephrine (1:1000) every two hours, aminophylline, atropine sulfate and coramine. With this treatment the ventricular rate remained slow and there was no reduction in the frequency of the syncopal attacks unless epinephrine was administered every two hours. Electrocardiograms taken on the following day (Fig. 2B) showed an irregular idioventricular rhythm with a rate of 12 to 28 per minute. Many of the beats were coupled with ventricular beats of different configuration which probably arose from another ventricular focus. The Q-T interval was extremely long, lasting 0.84 second.

Because of the onset of increasing dyspnea and signs of congestive heart failure, the patient was digitalized and received mercuhydrin injections. During the following days several attempts were made to reduce the frequency of epinephrine injections. An Adams-Stokes attack occurred each time the administration of the drug was delayed for more than two hours. It was then decided to continue this schedule. Only after three weeks was it possible to reduce the frequency of injection of aqueous epinephrine to every three hours and then to every four hours. Instructions were given to the nursing staff to administer epinephrine every two hours when the pulse rate slowed to 30 per minute or less. However, no further syncopal attacks occurred. After three months of hospital stay the patient was transferred to a hospital for chronic diseases.

CASE III. M. B., a fifty-seven year old housewife with long-standing rheumatic heart disease, mitral stenosis and insufficiency, and atrial fibrillation, entered the hospital on January 4, 1953, because of frequent syncopal attacks during the three weeks prior to admission. Three years before the patient had developed "fluttering" of the heart and electrocardiograms re-



3B 3C

FIG. 3. Case III. B, January 9, 1953. Records taken following a major Stokes-Adams attack treated with frequent doses of epinephrine. There is A-V dissociation with frequent ventricular ectopic beats forming short runs of ventricular tachycardia. C, February 2, 1953. A continuous tracing of lead II to illustrate the effect of a sublingual dose (7.5 mg.) of isuprel given while the patient was experiencing episodes of syncope due to ventricular asystole. The drug resulted in an almost immediate disappearance of ventricular asystole. A ventricular rate of 65 per minute with 2:1 A-V response was maintained.

vealed paroxysmal atrial flutter followed by chronic atrial fibrillation. She was treated with quinidine and digitalis and later kept on maintenance doses of digoxin.

Physical and x-ray examinations during the present admission confirmed the previous diagnosis of mitral stenosis and insufficiency. Electrocardiograms showed atrial flutter with an irregular atrial rate varying from 120 to 180 per minute. The ventricular rate was slow and irregular and averaged about 50 per minute, but occasionally slowed to 42 per minute. On January 6th the patient had a transient episode of syncope. Electrocardiograms taken during this episode (Fig. 3A) showed atrial flutter and periods of ventricular asystole lasting several seconds. Preceding and following this episode the ventricular rate was about 120 per minute with a 1:1 A-V response. During the following three days the patient sustained several major Adams-Stokes attacks with periods of unconsciousness and convulsions lasting from several seconds to several minutes. On one occasion the patient received an intracardiac injection of epinephrine with return of consciousness and increase in heart rate to 70 per minute.

The patient was treated during the acute syncopal episodes with epinephrine administered intramuscularly and she was given maintenance doses of atropine and epinephrine in oil by injection. Electrocardiograms taken following the injections of epinephrine showed numerous multifocal ventricular beats forming short runs of tachycardia. (Fig. 3B.) The drug was therefore more cautiously administered since it was considered that epinephrine might be increasing the frequency of Adams-Stokes attacks by causing ventricular acceleration and transient ventricular fibrillation. Moreover, the patient developed a sudden attack of left ventricular failure following an injection of epinephrine 1:200. It was then decided to discontinue epinephrine and to replace it with isuprel. This was administered sublingually in the form of one 15 mg. tablet every one to four hours. When the Adams-Stokes attacks became less frequent, the drug was continued prophylactically, in dosage of 7.5 mg. four times daily. She was also instructed to place an additional tablet under the tongue at the very first sign of an oncoming seizure. Usually the patient became aware of an impending attack by the onset of a feeling of lightheadedness, "blackout," or even transient fainting. Sublingual administration of isuprel was always effective in terminating the attacks. (Fig. 3C.) After several days in the hospital during which the dose of isuprel was adjusted to her needs, the patient was discharged home with a maintenance dose of this drug.

CASE IV. This seventy-seven year old white female (P. Y.) entered The Mount Sinai Hospital on December 27, 1953. Her present illness

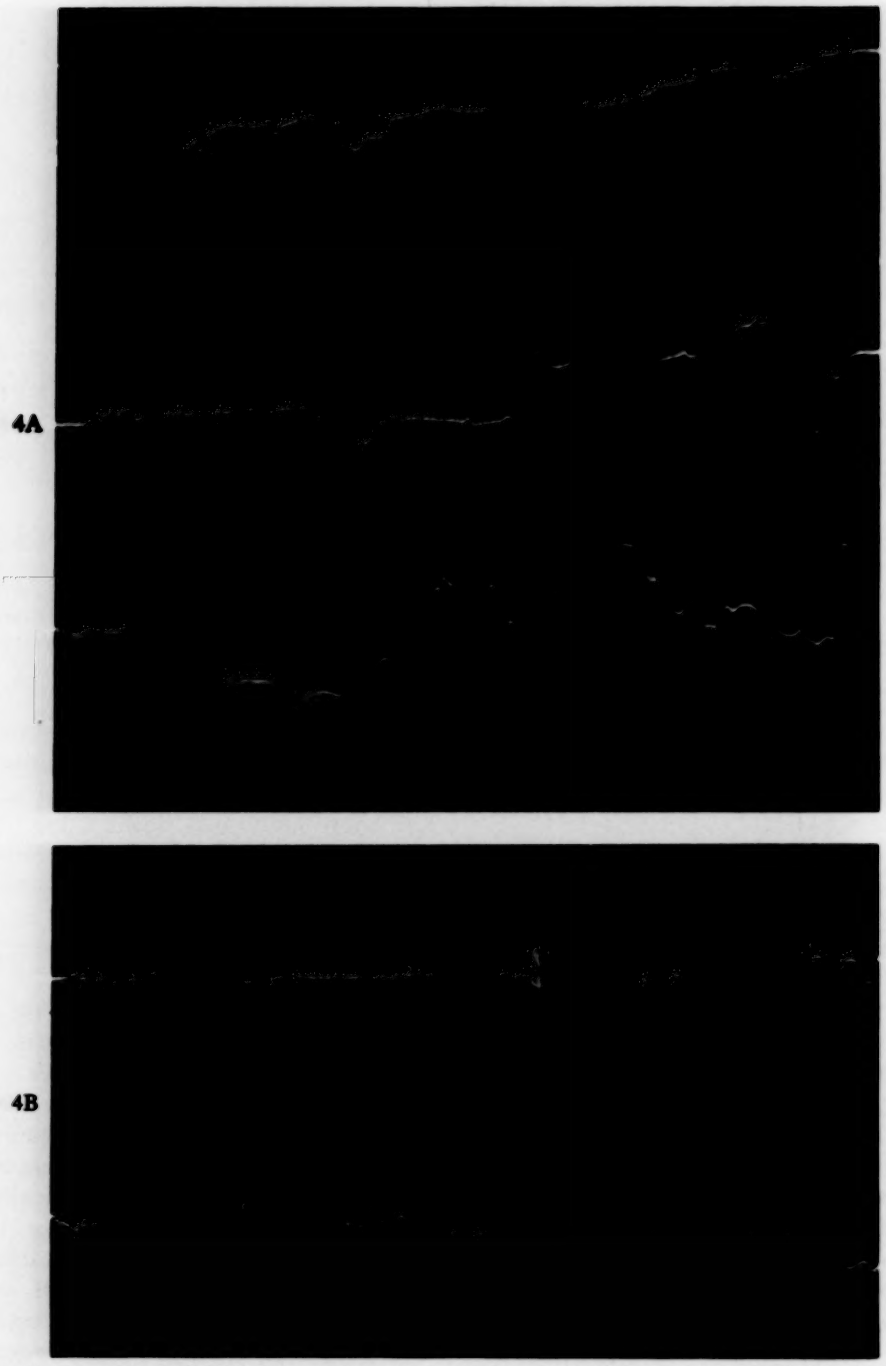
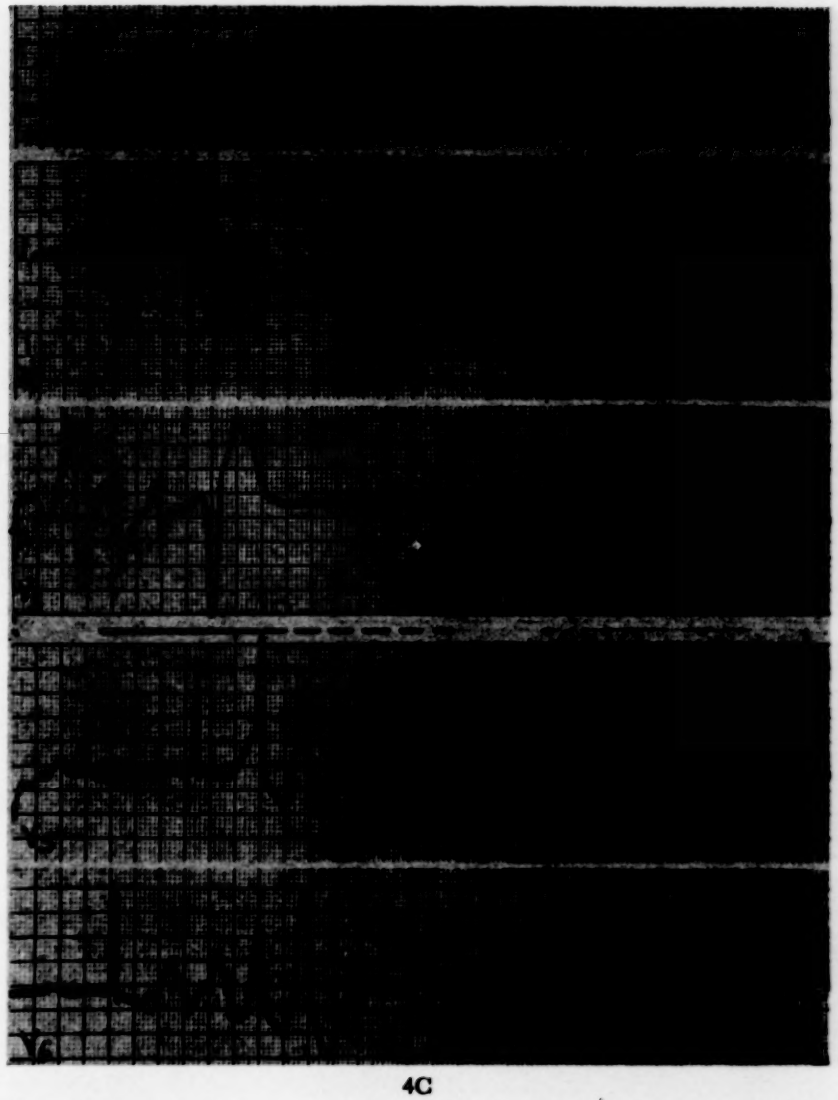


FIG. 4. Case IV. A, December 27, 1953, 3 P.M. Record on admission, showing complete A-V dissociation with frequent multifocal ventricular extrasystoles, occurring singly and in groups of two or three beats. B, December 27, 1953, 5 P.M. Continuous tracing of lead 3, taken during a period of unconsciousness, absent pulse and blood pressure. The record shows the basic mechanism of the Adams-Stokes attack to be ventricular fibrillation.

started two months prior to admission when she suffered an episode of unconsciousness followed by a period of hyperpnea, apnea and cyanosis. Similar episodes recurred two or more times daily for two weeks and usually lasted for about three minutes. The attacks occurred only rarely after that until the day of admission. After each attack the patient would be disoriented and agitated for a while. Her only medication consisted of 0.25 mg. of digoxin daily for the ten days prior to admission, and small doses of atropine and ephedrine all of which were with-

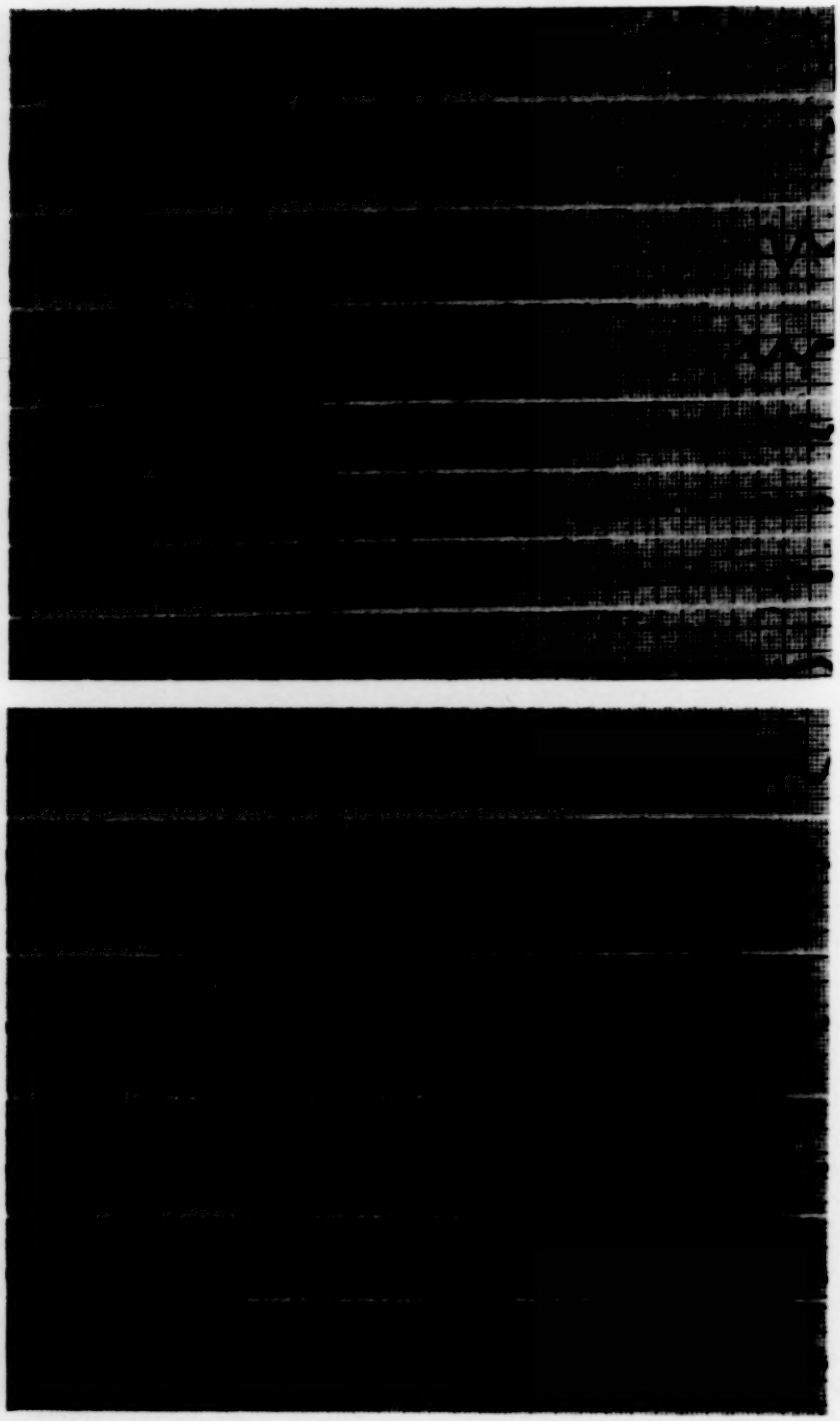


4C

FIG. 4C. Case IV. December 28, 1953. The record was taken after administration of quinidine in doses of 0.2 to 0.4 gm. intramuscularly every two to three hours. The record continues to show complete A-V dissociation with bursts of ventricular ectopic beats, forming runs of ventricular tachycardia of varying duration.

out any obvious effect. Her private physician stated that her pulse was found to be 40 beats per minute on one occasion.

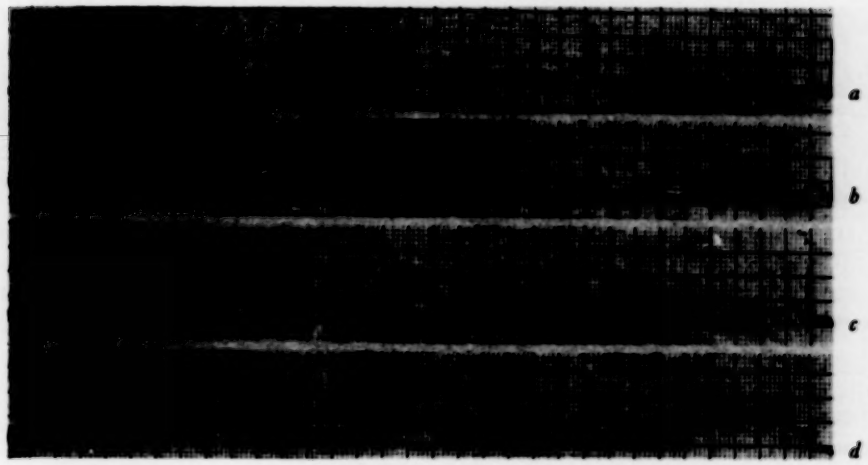
An episode of unconsciousness occurred immediately after admission to the hospital. For a period of twenty seconds no heart sounds were audible and the patient was unconscious. Thereafter the rate was 40 per minute and fairly regular. Physical examination revealed an elderly white female who was disoriented and uncooperative. The blood pressure ranged from 230/90 to 170/70. The rate was 44 and regular, except for an occasional extrasystole. The heart was enlarged to the left and there was a grade II blowing systolic murmur at the apex and aortic area. The electrocardiogram (Fig. 4A) at 3 P.M. on December 27, 1953, revealed complete atrioventricular block and frequent multifocal premature ventricular contractions, with occasional bursts of three beats in succession. Shortly thereafter a second tracing revealed prefibrillary contractions interrupting the basic rhythm episodically. No therapy was given until 5 P.M. when a record was obtained (Fig. 4B) which revealed a period of ventricular fibrillation occurring concomitantly with a two-minute period of unconsciousness, lack of pulse and unrecordable blood pressure. Upon recovery the patient became alternately confused and semicomatose. The heart rate returned to



4D

4E

FIG. 4. Case IV. D, December 29, 1953, 12 noon. Continuous tracing of lead I taken soon after Figure 4C during an Adams-Stokes attack. It shows the mechanism to be ventricular flutter and fibrillation (Strips A-D). Immediately following the cessation of fibrillation there is A-V dissociation with varying ventricular rate. Quinidine was discontinued following this attack. E, December 29, 1953, 5 P.M. Continuous tracing of lead I taken two hours following the administration of 0.5 gm. of procaine amide intramuscularly. The record shows recurrence of bursts of ventricular beats and runs of ventricular tachycardia.



4F

FIG. 4F. Case IV. December 29, 1953, 9 P.M. Continuous strip of lead II taken after cessation of quinidine and procaine amide therapy, and after administration of isuprel, 15 mg. sublingually every hour for four doses. The record shows sinus rhythm with normal A-V conduction (strips *a* and *b*) and periods of 2:1 A-V block (strips *c* and *d*).

approximately 40 beats per minute, with varying degrees of A-V block.

Treatment with quinidine sulfate intramuscularly was started and the patient received 1 gm. in divided doses from 5 P.M. to 11 P.M. Subsequent electrocardiograms continued to show frequent ventricular ectopic beats and recurrent bursts of ventricular tachycardia and fibrillation. (Fig. 4C.) The patient had four more severe attacks of syncope. The last attack resulted in coma from which the patient never recovered. She was then given 2.6 gm. of quinidine sulfate over the next twenty-two hours. There was no essential change in the electrocardiograms except for increased frequency of fibrillatory and pre-fibrillatory periods. (Fig. 4D.) The blood pressure gradually fell to 110/40 and remained stabilized at that level. The patient became anuric for twenty-four hours.

All drugs were stopped from 9 P.M. December 28th to 9 A.M. December 29th. At this time, about forty-two hours after admission, 0.2 gm. quinidine sulfate was given and repeated three hours later. Since there was no clinical response, it was decided to start procaine amide and accordingly, at 2:40 P.M., 0.5 gm. procaine amide was given intramuscularly. The electrocardiogram two hours later continued to show ventricular tachycardia and bursts of pre-fibrillatory beats. (Fig. 4E.) Isuprel was started sublingually at 6 P.M. and a 15 mg. tablet was given at hourly intervals until midnight. At 9 P.M. a tracing (Fig. 4F) revealed sinus tachycardia, rate 130 beats per minute, followed by 2:1 A-V block with a ventricular rate of 70 per minute. Although an order had been left to discontinue procaine amide, another dose of 0.5 gm. was administered by error at 9 P.M. This was followed by another short episode of ventricular tachycardia. Because of persistent hypotension and anuria, nor-epinephrine was started intravenously at 10:50 P.M. with a resultant rise in blood pressure to 170/70. In the following twenty-four hours the urinary output was 1,050 cc. and the nor-epinephrine was then discontinued. The morning after the cardiac rhythm had been converted to sinus rhythm (December 30, 1953) the electrocardiogram still showed periods of 2:1 A-V block alternating with sinus tachycardia. Isuprel was again started sublingually in 15 mg. doses at two- to three-hour intervals and the A-V block disappeared. The following day isuprel was discontinued but was restarted when the 2:1 A-V block reappeared. From then on until her death forty-eight hours later (January 2, 1954) administration of isuprel was continued every two to three hours and the electrocardiogram showed persistent sinus rhythm.

Autopsy revealed a large heart which weighed 450 gm., with predominant left ventricular hypertrophy. There was no evidence of recent or old myocardial infarction. There was severe atherosclerosis of the aorta, diffuse bilateral bronchopneumonia and moderate congestion of the liver. Microscopic studies of the heart muscle revealed areas of focal myocardial fibrosis.

COMMENTS

The mechanisms initiating Adams-Stokes attacks in these four patients with complete heart block were different, indicating the importance of the individual approach to management of the Stokes-Adams syndrome. No one form of standardized treatment can be applied effectively to all cases, and attempts to do so may prove hazardous in some instances.

The first case indicates that in certain instances when syncopal attacks are infrequent administration of the usually recommended drugs is not beneficial except during periods of ventricular standstill. The patient's condition appeared to become aggravated by vigorous treatment with epinephrine, ephedrine or barium chloride. When the heart block becomes stabilized and a fixed idioventricular pacemaker is established, specific therapy may be unnecessary or ineffective. This is particularly true if the ventricular rate remains at 40 per minute or over, as it did in this case for a period of six years. Such a patient should be observed periodically for changes in the cardiac pacemaker or undue slowing of the heart rate, but requires no other treatment.

In the second case, in which ventricular asystole was the responsible mechanism, administration of epinephrine was life-saving. This drug had to be given every two hours during the first three weeks, in addition to aminophylline and atropine, to prevent Adams-Stokes seizures. A decrease in the frequency of injections of epinephrine from every two hours to every three to four hours always resulted in recurrence of the attacks. We were dealing here with a patient whose idioventricular pacemaker was very depressed. Fortunately, the irritability of his myocardium also was decreased. Under constant electrocardiographic control epinephrine was safely and effectively administered despite the enormous doses which had to be employed. At no time were paroxysms of ventricular tachycardia or numerous ventricular ectopic beats observed during this treatment. Atrial flutter and fibrillation occurred during the early days of intensive treatment but later disappeared.

In the third case the mechanism producing Adams-Stokes attacks appeared to be ventricular asystole in the course of atrial flutter. Administration of epinephrine, however, invariably produced bursts of ventricular extrasystoles or short runs of ventricular tachycardia, indicating marked myocardial irritability. While effectively stimulating the idioventricular pacemaker, epinephrine at the same time produced multiple ventricular ectopic beats or even prefibrillatory ventricular tachycardia by exciting lower ventricular unstable foci. Consequently, this drug could abolish the ventricular standstill but at the same time precipitate ventricular fibrillation and thus perpetuate the Stokes-Adams seizures. Of further interest in this case were the changing atrial rhythms observed during the hospital stay. The chronic atrial fibrillation present for several years prior to admission was observed to change to atrial flutter or tachycardia with an irregular and varying atrial rate. In the same record and in records taken on different days the atrial flutter rate showed considerable variation, ranging from 110 to 300 per minute. This was observed best during the periods of ventricular asystole.

In the fourth and final case there was definite electrocardiographic evidence that ventricular tachycardia and fibrillation initiated the Adams-Stokes attacks. The course of events suggested that both quinidine and procaine amide contributed to perpetuating the ventricular fibrillation. After administration of isuprel there was complete cessation of ventricular tachycardia and fibrillation and of the Adams-Stokes seizures. Moreover, we were able to observe a definite change in the rhythmic action of the heart. There was a reversion to regular sinus rhythm or partial 2:1 heart block. Although cessation of the ventricular tachycardia four hours following the administration of isuprel may have been coincidental, or due to the withdrawal of quinidine and procaine amide, we believe that the isuprel aided in restoration of a normal ventricular pacemaker.

These cases illustrate the importance of distinguishing between the two different cardiac mechanisms responsible for initiating Adams-Stokes attacks in a patient with complete heart block: (1) ventricular asystole, (2) ventricular tachycardia and ventricular fibrillation. Treatment should be guided by electrocardiographic analysis of the causal mechanisms.

Epinephrine has been recommended as the drug of choice when the attacks are due to ventricular asystole and in patients with this mechanism the clinical effect of the drug is good if it is administered in sufficient dosage (Case II). In recent years, however, there is mounting

evidence that in certain patients epinephrine may act not only on the main ventricular pacemaker but may incite the lower ventricular foci as well. This may precipitate ventricular tachycardia or even fibrillation. Moreover, it is not unusual for the same patient to exhibit one mechanism at one time and another later, ventricular tachycardia alternating with ventricular asystole. This points up the danger of indiscriminate use of epinephrine in the treatment of Adams-Stokes attacks without frequent electrocardiograms to check the progress of events.

When ventricular tachycardia or fibrillation causes cardiac standstill the use of quinidine or procaine amide theoretically would seem to be advisable for prevention of the attacks. Experience in recent years, however, has shown that there is some danger involved in the use of these drugs. Quinidine may be effective in abolishing ventricular tachycardia but in the presence of complete heart block, bundle branch block or intraventricular block it may precipitate ventricular fibrillation or asystole. Similarly, procaine amide may be capable of stopping ventricular fibrillation by its depressant action on the ventricular myocardium. At the same time, however, it depresses the rhythmicity of the heart and the region of the junctional tissues which may, after termination of the fibrillation, cause ventricular standstill. In certain instances procaine amide may, in the presence of heart block, induce ventricular fibrillation.

Isuprel has a stimulating effect on the active ventricular pacemaker of the heart without inciting the lower potential ventricular foci at the same time and therefore, in contrast to epinephrine, does not predispose the heart to ventricular fibrillation or tachycardia. Furthermore, when administered to patients with Adams-Stokes attacks associated with ventricular tachycardia or fibrillation isuprel not only has no apparent deleterious effects but also may aid in preventing recurrence of attacks by stimulating the higher rhythmic centers of the heart. Moreover, unlike quinidine and procaine amide, it does not have a depressant action on the junctional tissues or myocardium. Indirectly, by increasing the rate of effective heart beats and therefore the total duration of the refractory period of the ventricular myocardium, isuprel may make ventricular fibrillation less likely. For these reasons, isuprel may be considered the safest drug for use in the Adams-Stokes syndrome when the exact cardiac mechanism of the attacks cannot be established electrocardiographically or when both mechanisms are observed to operate in rapid succession in the same patient. In contrast to other sympathicomimetic drugs, isuprel has little or no pressor action, consequently it may be used in patients with marked hypertension when ephedrine or epinephrine may be dangerous.

Isuprel is administered sublingually, has a rapid absorption time, and acts quickly. The usual dose for the prevention of attacks is 10 to 15 mg. sublingually, four to five times daily. For treatment during attacks the frequency of administration and the dosage must be increased but this varies in different patients and even in the same patient depending upon the patient's tolerance and requirements. In Case IV it was necessary during the first twenty-four to forty-eight hours of treatment to give as much as one 15 mg. tablet every hour to prevent recurrence of attacks. After the number of attacks was reduced the prophylactic dose was readjusted. In another patient (Case III) the optimal dose was 7.5 mg. four times daily. A larger dose produced unpleasant side effects such as forceful and rapid heart rate and dizziness.

On several occasions we have been able to observe and record electrocardiographically the rapid action of isuprel in preventing an impending attack of Adams-Stokes seizures. (Fig. 3C.) Therefore, it is advisable that patients receiving prophylactic isuprel be instructed to take an additional dose as soon as they feel the premonitary symptoms of an oncoming seizure. Some patients develop a tolerance to the drug when it is taken for a long period of time and the dose or frequency of administration may have to be increased.

A stable solution of isuprel for parenteral administration would be advantageous for patients with rapidly recurrent major attack of Stokes-Adams syndrome. In such cases repeated intramuscular injections or slow intravenous infusion could tide the patient over the emergency period until a more stable cardiac pacemaker is established.

SUMMARY

1. Four cases of heart block with Stokes-Adams syndrome are presented to illustrate the two different mechanisms which may precipitate the attacks, namely, ventricular asystole and ventricular tachycardia or fibrillation. Empha-

sis is placed on individualization of treatment, which is adjusted according to the underlying mechanism.

2. Epinephrine is the drug of choice for the treatment of ventricular asystole and should be administered in sufficient dosage under electrocardiographic control. It is contraindicated when ventricular tachycardia or fibrillation is the mechanism for the attacks.

3. Procaine amide and quinidine have been found to be ineffective and even harmful in the treatment of ventricular tachycardia or fibrillation in the presence of heart block. This is due to their depressant effect on the junctional tissues.

4. The effect of isopropyl norepinephrine (isuprel) in two cases of Stokes-Adams syndrome is described. In one case the causal mechanism was ventricular asystole and in the other, ventricular fibrillation. Isuprel stimulates the higher ventricular centers and therefore does not predispose to ventricular fibrillation. It appears to be the drug of choice when the basic mechanism for the Stokes-Adams syndrome is ventricular tachycardia or fibrillation and when ventricular asystole alternates with tachycardia or fibrillation in the same patient.

5. Three of the cases exhibited atrial flutter in association with the A-V block, a rare combination.

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Idiopathic Recurrent Pericarditis*

Comparison with the Postcommissurotomy Syndrome; Considerations of Etiology and Treatment

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THERE are numerous reports in recent years about idiopathic pericarditis.[1-38] The title does not reflect the complex nature of the disease which actually represents polyserositis as well as pneumonitis. Wolff drew attention to the frequent occurrence of pleurisy which greatly aids in the differential diagnosis of benign pericarditis and coronary attacks.[10] Several writers stressed the association of idiopathic pericarditis with atypical pneumonia.[2,8,18,26] Indeed, involvement of the lungs as reported by many students[4,6,7,11,13,15,30-32] of the syndrome and observed by the writer is frequent enough to indicate more than a fortuitous association. Certain observations suggest that myocarditis is a significant feature in some of the cases.[34]

On studying patients who underwent mitral commissurotomy the writer was impressed with the similarity of clinical and laboratory features in the postcommissurotomy syndrome and in idiopathic pericarditis. This observation revived interest in the problems of etiology and treatment of so-called idiopathic pericarditis.

It is the purpose of this paper first to stress the complex nature of the disease which is usually termed idiopathic, non-specific or benign pericarditis, and to point out the significance of associated pleurisy or pneumonitis in the differential diagnosis of pericarditis and acute coronary attacks; second, to compare idiopathic pericarditis with the postcommissurotomy syndrome; and third, to reconsider the etiology and treatment of so-called idiopathic pericarditis.

OBSERVATIONS OF PATIENTS WITH IDIOPATHIC PERICARDITIS

Twelve patients were studied in whom the diagnosis of idiopathic pericarditis was made, based on the findings of a pericardial friction rub, electrocardiographic or roentgenologic evidence, and absence of known etiologic factors. The clinical and laboratory features of idiopathic pericarditis have been adequately described by others.[1-3] Our own observations are summarized in Table I. Severe and sometimes excruciating pressure or pain felt across the chest, in the neck, shoulders, arms, lower chest or upper abdomen, aggravated by breathing or motion, represented the leading symptoms. Fever, leukocytosis and increased sedimentation rate were almost invariably present. In cases with protracted course or frequent relapses moderate anemia and hypoproteinemia developed. Nine patients had, in addition to pericarditis, x-ray evidence of pleurisy, which in seven instances was on the left and in two cases bilateral but predominating on the left side. Pericardial and pleural effusions were usually small. Three patients had pneumonitis. In two cases myocardial involvement was suggested by transient occurrence of auricular fibrillation, gallop rhythm or congestive heart failure. In one of these patients gallop rhythm and congestive heart failure quickly subsided together with the manifestations of pericarditis and pleurisy. In the other case congestive heart failure outlasted the pericarditis for several weeks. Similar observations were reported by Godfrey who expressed doubt as to whether a benign course is typical of all instances of idiopathic pericarditis.[34]

A tendency to recurrence is a prominent feature of the disease. Relapses occurred in half of our cases, twelve patients suffering a total of forty-two attacks. A boy of fourteen had nine attacks within four years; a woman of forty-five had seven episodes of pericarditis and pleurisy within seven months; another woman, aged

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TABLE 1

OBSERVATIONS IN 12 CASES OF IDIOPATHIC, RECURRENT PERICARDITIS

Case No.	Name, Sex and Age	No. of Attacks	Associated Pleurisy and Pneumonitis	Rheumatic Manifestations in		Laboratory Data	Response to Treatment	Remarks
				Patient	Family			
1	J. C., M, 14	9 (1950–1954)	Pleurisy, left			ECG consistent with pericarditis; leukocytosis; elevated sedimentation rate; high antistreptolysin titer in some attacks	Favorable response to phenylbutazone	
2	J. M., M, 23	1 (Dec. 1953)			Mother has rheumatic heart disease	ECG consistent with pericarditis; leukocytosis; elevated sedimentation rate; normal antistreptolysin titer	Spontaneous improvement	
3	A. J. G., M, 31	3 (Sept.–Oct. 1953)	Bilateral pleurisy and pneumonitis		Nephew had rheumatic fever	ECG consistent with pericarditis; leukocytosis; elevated sedimentation rate; normal antistreptolysin titer	No response to aureomycin; favorable response to aspirin	At age 17, pleurisy; during pericarditis, gallop rhythm and congestive heart failure; rapid complete recovery
4	I. P., M, 39	1 (Oct. 1952)		At age 15 rheumatic fever, mild mitral stenosis		ECG consistent with pericarditis; leukocytosis; elevated sedimentation rate	Spontaneous improvement	Pleurisy several years prior to pericarditis
5	J. W., F, 44	9 (Feb. 1953–March 1954)	Pleurisy, left	As a child frequent epistaxis		ECG consistent with pericarditis; leukocytosis; elevated sedimentation rate; mild anemia	Favorable response to pyramidon	Sedimentation rate remained elevated in periods between attacks
6	E. K., F, 45	7 (Oct. 1953–Apr. 1954)	Pleurisy, left			ECG consistent with pericarditis; no leukocytosis; elevated sedimentation rate; eosinophilia in pleural effusion	Severe chest pain promptly eliminated by aspirin but not by demerol	Sedimentation rate remained elevated in periods between attacks
7	C. F., M, 49	4 (Sept. 1952–June 1953)	Pleurisy, left, and pneumonitis			ECG consistent with pericarditis; leukocytosis; elevated sedimentation rate	Antibiotics had no effect	
8	S. G., M, 57	1 (Jan. 1951)		Rheumatic valve lesions (MI,AI)		ECG consistent with pericarditis; leukocytosis; elevated sedimentation rate; normal antistreptolysin titer	Spontaneous improvement	Pain localized primarily in upper abdomen initially diagnosed acute abdominal condition
9	R. G., F, 57	1 (Nov. 1953–March 1954)	Bilateral pleurisy, predominantly left		Sister died of "heart trouble," age 15; brother died of "heart trouble and rheumatism," age 28	ECG consistent with left ventricular strain and pericarditis; leukocytosis; elevated sedimentation rate; marked anemia; hypoproteinemia; normal antistreptolysin titer	Dramatic response to aspirin as well as to pyramidon	Diabetes, hypertension; transient atrial fibrillation; congestive heart failure coincident with serositis; elevated sedimentation rate and congestive heart failure outlasted other manifestation of serositis
10	S. O., F, 58	4 (Oct. 1953–March 1954)	Pleurisy, left, pneumonia	Polyarthritis for more than 30 yr.	Nephew has rheumatic heart disease; Mother and sister suffer from polyarthritis	ECG consistent with left ventricular strain and pericarditis; leukocytosis; moderate anemia; elevated sedimentation rate	Favorable response to pyramidon	Hypertension; transient atrial fibrillation coincident with third attack of pericarditis
11	P. S., M, 59	1 (Feb. 1954)	Pleurisy, left		Sister has rheumatic heart disease	ECG consistent with pericarditis; leukocytosis; elevated sedimentation rate; mild anemia; elevated antistreptolysin titer	Favorable response to pyramidon	Hypertension; after clinical improvement anemia and elevated sedimentation rate persisted
12	J. F., M, 65	1 (March 1954)	Pleurisy, left			ECG consistent with pericarditis; leukocytosis; elevated sedimentation rate	Spontaneous improvement	

forty-four, suffered nine attacks within thirteen months. Frequent relapses occurring at short intervals greatly tax the endurance of the patients and call for swift and effective therapy.

The age of the patients in this series ranged from fourteen to sixty-five, averaging forty-five years. Two-thirds of the patients were over forty years of age. Many writers have commented on the fact that acute pericarditis may simulate a coronary attack and discussed signs helpful in the differential diagnosis. Those features favoring pericarditis are: occurrence of pain of the pleuropericardial type, fever, pericardial friction rub and increased sedimentation rate on the first day of the attack; in the electrocardiogram, the finding of an elevated S-T segment in leads AVL and AVF and in all standard extremity leads; and absence of significant changes of QRS. In occasional instances, however, great diagnostic difficulties are encountered, especially when the patient is not seen early in the disease and no adequate history can be obtained. In five of our patients coronary occlusion was diagnosed at first, and in two instances the true nature of the disease was not recognized until several relapses had occurred. It is in such cases that the differential diagnosis may be greatly facilitated by the finding of pleuritis or pneumonitis accompanying the pericarditis. This is illustrated by the following case report:

CASE I. C. F., a forty-nine year old man, was first examined on October 29, 1952. Five weeks previously he was suddenly seized by severe pain across the chest which lasted for an hour and was terminated by an injection of a narcotic. It was not aggravated by breathing or motion of the body. Pain did not recur in the following weeks. The attack was followed by rise in temperature which lasted for four days. An electrocardiogram taken one day after the attack of pain showed elevation of the S-T segment in leads I, AVL, V_5 and V_6. A cardiologist diagnosed acute coronary occlusion. Subsequent tracings showed return of the S-T segments to the base line and development of low, notched T waves. The diagnosis was then changed to coronary insufficiency. The patient was kept in bed for four weeks. Occasionally he complained of a sensation of mild pressure in the left subclavicular area.

On examination five weeks after the attack the patient presented no abnormal physical findings. The electrocardiogram had returned to normal. Roentgen study of the chest revealed haziness at the base of the left lung which was interpreted by the roentgenologist as resolving pneumonitis. The serum cholesterol was 176 mg. per cent. No history of previous pain of the anginal type was elicited. Evidence for an acute coronary attack was held to be inconclusive, and benign pericarditis was considered a distinct possibility.

The patient continued to complain about vague pressure sensations in various parts of the chest occurring usually after meals or when the patient talked much. Nitroglycerine did not relieve the discomfort. On March 28, 1953, the patient experienced pain across the chest quite similar to the first attack. Four days later chest pain recurred and was for the first time aggravated by breathing. The temperature was increased for six days. A chest specialist diagnosed pleural effusion and pneumonitis. A similar attack occurred on May 6, 1953, with identical roentgenologic findings. There were no electrocardiograms taken during the last two attacks.

On June 19, 1953, the patient again felt severe pain in the left side of the chest, which was accentuated on deep inspiration. The pain was only partly relieved by hypodermic injection of demerol. It recurred on the following days and fever developed. An electrocardiogram showed the same changes of S-T-T as during the first attack which occurred nine months previously. It was then clear that the patient was suffering from relapsing benign pericarditis, pleurisy and pneumonitis. In the following months the patient was able to resume his routine activities. There was no further relapse. When the patient was re-examined eighteen months after the initial attack there were no abnormal physical findings. Occasionally, dull pressure in the chest was brought on by talking. The capacity for effort was satisfactory.

Comment. A forty-nine year old man suffered four attacks of pericarditis, pleurisy and pneumonitis within a period of nine months. Coronary occlusion was first diagnosed. The true nature of the condition might have been recognized during the first attack if proper attention had been paid to the findings of pleurisy and pneumonitis, which were associated with electrocardiographic abnormalities suggestive of pericarditis.

OBSERVATIONS OF PATIENTS WITH THE POSTCOMMISSUROTOMY SYNDROME

A febrile syndrome following mitral commissurotomy was described by Soloff and associates.[39] Pain in the chest aggravated by breathing and motion was a prominent symptom.

X-ray study revealed enlargement of the cardiac silhouette and indistinct demarcation of the contours of the heart chambers. The electrocardiogram showed changes of the S-T segment suggestive of pericarditis, occasional prolongation of the P-R interval and other features indicative of "myocardial derangement." Relapses occurred frequently. The authors pointed out that a similar syndrome was not observed following pulmonary or cardiac surgery in nonrheumatic patients. Therefore, and because the heart was apparently involved, the condition was regarded as reactivation of rheumatic fever precipitated by surgery. The authors referred to reports that trauma could precipitate rheumatic activity and determine the localization of the rheumatic process.[40–44] With regard to the dominant role of pain in the postcommissurotomy syndrome, Soloff and associates pointed out that chest pain was known to occur in rheumatic fever but "the greater incidence and greater severity of pain in this syndrome than that in naturally occurring clinical activation may be related to the greater involvement of the parietal pericardium." Joint pains, hemoptysis, psychoses and various arrhythmias occasionally accompanied the syndrome. Congestive heart failure developed frequently, ending fatally in three instances. The prognosis of the postcommissurotomy syndrome was therefore regarded as serious.

Our own observations include seventy-six bouts of postcommissurotomy syndrome which occurred in twenty-four patients. The syndrome was observed in 40 per cent of the patients operated upon for mitral stenosis; this incidence was later reduced by introduction of prophylactic treatment with cortisone.[45] In two-thirds of the patients the complication occurred within a month of the operation. In the remaining cases the first attack followed the operation after an interval of from six weeks to six months. On occasions, however, the exact date of onset was ill defined, particularly when the postoperative pleural reaction was unusually severe and a large pleural effusion developed. Postoperative fever did not subside as usual after a few days. The characteristic pain, however, did not appear until some weeks later, during a relapse of the syndrome.

As in Soloff's cases, chest pain which was aggravated by breathing or motion was the most significant feature. It was variously described as a choking, tightening or pressing sensation, or as knife-like, shooting, throbbing, "like a tooth ache." The pain was usually severe, even excruciating, and interfered with proper breathing so that the patient sometimes complained of shortness of breath. In a minority of cases the pain was mild, merely a "soreness" or "raw feeling." This happened especially in patients with frequent relapses during which the intensity of the pain often diminished. In a few instances, however, pain was absent during the first or second bout but appeared with great violence in subsequent attacks. Pain was felt usually across the upper half of the chest; other localizations were the neck, back, shoulders, arms, lower chest and abdomen. In some instances x-ray studies of the gastrointestinal tract and gallbladder were carried out because of predominant localization of pain in the epigastrium. In one patient severe abdominal distress and distention resulted in exploratory laparotomy. Shortness of breath occurred in patients with extensive pulmonary involvement.

In many instances a short period of chest pain preceded the onset of fever which was sometimes accompanied by chills. Fever ranged usually from 100° to 102°F. but sometimes reached peaks of 104°F. In cases with protracted course the fever was usually of an irregular type, high peaks alternating with dips of the temperature to 100°F. or below. Fever was sometimes absent when repeated relapses occurred

Clinical and laboratory evidence usually pointed to the presence of pleurisy which was variously associated with pericarditis or pneumonitis. Pleurisy was most often on the left. Effusions were rarely marked enough to require paracentesis. Involvement of the pericardium was indicated more often by chest pain and friction rub rather than by roentgenologic signs. Electrocardiographic signs of pericarditis, except for inversion of T, were usually missing when other features, including pain and pericardial friction rub, pointed to pericarditis. It is difficult to say whether the significant changes in the electrocardiogram were masked by digitalis effect[46] which was routinely given after the operation, or whether uniform involvement of the pericardium caused the injury patterns around the heart to neutralize one another.[33] In seven patients there were clinical and roentgen signs of pneumonitis, associated with pleurisy or pericarditis.

Leukocytosis was observed in nearly every case of postcommissurotomy syndrome. In four

instances the white blood count rose to values ranging from 21,000 to 31,000 per cu. mm. Mild anemia and hypoproteinemia developed, especially in cases with a protracted course. The erythrocyte sedimentation rate, as a rule, was elevated. The antistreptolysin O titer was tested in fourteen patients; it was normal in eleven and increased in three, reaching values of from 333 to 1,250 units. Cultures of blood and pleural effusion were negative. In one patient a single blood culture showed growth of Streptococcus viridans, in the absence of other evidence of bacterial endocarditis.

Relapses of the postcommissurotomy syndrome were observed in 75 per cent of the patients; most of them had two or three attacks. Two patients suffered seven attacks and one patient had twelve attacks in the course of eighteen months following operation. The intervals between relapses ranged from ten days to two months; in exceptional cases ten and twelve months elapsed between episodes of postcommissurotomy syndrome. The attacks were self-limited, lasting from six to eight days, as a rule. There were, however, bouts of one or two days' duration, while other episodes were unusually prolonged extending over periods of several weeks or even months. In the latter cases fever and pain showed short remissions, making it difficult indeed to know whether we were dealing with a single long episode or with multiple bouts which rapidly followed one another.

As to etiology, we agree with Soloff and his group that there are compelling reasons for the belief that the postcommissurotomy syndrome is a manifestation of rheumatic activity. Exudative, benign processes predominate. Neither psychoses nor hemoptysis was observed in this series. Auricular fibrillation occurred as a transient phenomenon; it was readily controlled by digitalis and converted to normal rhythm by quinidine. Right heart failure was observed in nine patients all of whom had been treated for congestive failure prior to surgery. There were no fatalities in this series, nor did the complication seem to affect the final outcome of the operation. In twelve cases the results of surgery were exceedingly satisfactory, even though some of the patients had suffered repeated, severe attacks of postcommissurotomy syndrome. Thus the prognosis of the postcommissurotomy syndrome appeared to be more favorable in this series than in the larger group of cases reported by Soloff and associates. The difference possibly is explained by the intensive and prolonged treatment with cortisone which was employed in many of our cases.[45]

We know of no feature in the preoperative state which might have enabled us to predict whether or not the postcommissurotomy syndrome would develop in any given case. The difficulty of determining the presence or cessation of activity of the rheumatic process is well known. Prior to surgery many of our patients presented one or another feature such as low-grade fever or leukocytosis usually associated with rheumatic activity. Yet there was no clear parallelism between the presence of such features and the incidence of the postcommissurotomy syndrome. Some patients in whom surgery was performed because of embolic events failed, in spite of strong evidence of rheumatic activity, to develop the postcommissurotomy syndrome, whereas this complication occurred in others who were apparently free of signs of active rheumatic infection. Nor was a definite relationship observed between the findings of Aschoff bodies in the resected left atrial appendage and the incidence of the postcommissurotomy syndrome.

Antibiotics failed to influence the course of the postcommissurotomy syndrome. In a few patients administration of aureomycin or terramycin® was followed by improvement. However, evaluation of the effect of drugs is difficult in a condition which is usually self-limited and may not last longer than five or six days; hence spontaneous termination might readily simulate success of treatment. Salicylates were used in a small number of cases; in some, fall of temperature and cessation of pain occurred but more often salicylates did not appreciably alter the course of the complication. Pyramidon® seemed to be more beneficial. Cortisone proved to be the most effective and dependable treatment when adequate dosage was used.[45]

ETIOLOGY OF SO-CALLED IDIOPATHIC PERICARDITIS

Idiopathic pericarditis and the postcommissurotomy syndrome show a striking resemblance of clinical and laboratory features. Both are complex conditions comprising pericarditis, pleurisy and pneumonitis. There is evidence of involvement of the myocardium in some of the patients. Pain of the pleuropericardial type is a prominent feature. Fever, leukocytosis and rapid sedimentation of the red blood cells are common to both syndromes. The course is

almost invariably benign. Relapses occur frequently. In some cases idiopathic pericarditis was reported to have followed surgery.[1,13,16,17] Since "non-specific" pericarditis resembles closely the postcommissurotomy syndrome, which is thought to be a manifestation of rheumatic activity,[39] re-examination of the etiology of so-called idiopathic pericarditis seems to be in place.

The cause of idiopathic pericarditis is still obscure. A virus was thought to be the responsible agent[2,6,28,37] because idiopathic pericarditis often followed upper respiratory infections and seemed occasionally to respond to aureomycin.[28] Some authors have commented on the resemblance of idiopathic pericarditis to Bornholm disease, epidemic pleurisy and myositis epidemica.[15,47–49] Immunologic tests for various kinds of virus, including several strains of Coxsackie virus, gave negative results.[7,15,28,30] Tuberculosis is unlikely to be the etiologic factor because there are marked clinical differences between idiopathic and tuberculous pericarditis.[3,14] Examinations of sputum and gastric washings for acid-fast bacilli were invariably negative. Cultures of blood, pericardial and pleural effusions remained sterile. Allergy was blamed in a case in which a personal and family history of allergy was elicited and a high eosinophil count was observed in the pleural exudate.[32] The contention of an allergic etiology was never proven. Eosinophilia in pleural effusions has been found in eighteen different kinds of pleurisy and does not imply a specific etiology.[50]

Nathan and Dathe[25] held that non-specific pericarditis represented a "hypersensitive response by the pericardium to an offending organism in which the immune reaction of the body is inadequate," in this respect resembling the rheumatic state for which a similar explanation has been offered. Indeed, idiopathic pericarditis has many features in common with rheumatic fever. Both conditions are frequently preceded by upper respiratory infections. They show great susceptibility to relapse. Increase of the erythrocyte sedimentation rate often persists when clinical data seem to indicate return to the inactive state. In three of our cases of idiopathic pericarditis subclinical activity between relapses was suggested by a high erythrocyte sedimentation rate when other manifestations of the condition had subsided. Idiopathic pericarditis, like rheumatic pericarditis is often associated with pleurisy which is preferentially localized on the left.[1,46,51,52] Pleural and pericardial effusions are rarely copious. When pericardial effusion does occur, it may be of hemorrhagic character in idiopathic as well as in rheumatic pericarditis.[25,36,52–54] Neither idiopathic nor rheumatic pericarditis have a tendency to develop into constrictive pericarditis.[3,55*]

Christian,[37] commenting on idiopathic pericarditis, stated: "In its various clinical phenomena it is more the rheumatic type than any other . . . " Indeed, on occasion it is impossible to differentiate idiopathic from rheumatic pericarditis.[13,26] Yet, clinical investigators have been almost unanimous in rejecting a rheumatic etiology for non-specific pericarditis,[1–3,7,11,15,23,24,28,37] for the following reasons: Patients suffering from idiopathic pericarditis fail to show other criteria of rheumatic fever.[7,15] Rheumatic pericarditis is usually part of a pancarditis, whereas in idiopathic pericarditis evidence of myocardial and endocardial involvement is lacking, and after healing there is no residual heart disease.[2,6,7,26] Furthermore, serologic evidence in support of a rheumatic infection is lacking in idiopathic pericarditis.[7,11,23] Of particular significance is the marked difference in the course and outcome of the two conditions. Idiopathic pericarditis is a benign disease. In contrast, rheumatic pericarditis has a protracted course often marked by congestive heart failure and fatal outcome.[11,15,26] In fact, the high mortality rate of children suffering from rheumatic pericarditis has been cited as conclusive proof that we are dealing with two different disease processes.[7]

Some of these arguments would appear to be based on erroneous interpretation of observations made in children who succumbed to rheumatic fever.[54,55] Postmortem study revealed, in 55 per cent of these patients, acute inflammation of the pericardium associated with myocarditis and endocarditis.[55] From this the conclusion was drawn that rheumatic pericarditis is part of a pancarditis and of grave prognosis. This view disregards reports on healing of rheumatic pericarditis without residual damage to the heart.[53,56–58] Massie and Levine[57] showed that such a favorable outcome was by no means infrequent. Among 135 patients with rheumatic pericarditis who were followed up for

* In a recent paper benign pericarditis was reported to have turned into constrictive pericarditis. The evidence offered for this diagnosis was not convincing. (Rabiner, S. F., Specter, L. S., Ripstein, C. B. and Schlecker, A. A. Chronic constrictive pericarditis as sequel to acute benign pericarditis. *New England J. Med.*, 251: 425, 1954.)

periods from one to seventeen years, twenty-two died during the acute infection and twelve succumbed later to heart disease. On the other hand, of eighty-two surviving patients whose follow-up data were available, fifty-two were found to be in a satisfactory condition and able to carry on essentially normal activities. Twenty-five patients showed no residual heart disease. The authors remarked: "It follows that even after a severe bout of rheumatic pericarditis recovery can frequently be so complete that years later there may be no signs or symptoms of heart disease." Mosler reported on fifteen cases of rheumatic pericarditis and pleurisy, ten of which healed without residual heart disease.[56] The essentially benign character of the post-commissurotomy syndrome, believed to be of rheumatic origin, has already been pointed out.

The contradictory views expressed by various investigators as to the prognosis of rheumatic pericarditis are probably explained by the factor of age.[59,60] In children rheumatic pericarditis carries a high mortality rate, whereas a favorable outcome was reported in studies which included adult age groups. The age of the patients studied by Massie and Levine[57] ranged from three to fifty-seven years, and averaged 19.6 years. Mosler[56] stated that the prognosis of rheumatic pericarditis was more favorable the more the age of the patients had advanced beyond puberty. Findlay and associates[58] reported a fatal outcome in twenty-six of fifty-one cases of rheumatic pericarditis occurring in children. On the other hand, they quoted Gairdner as stating that he had never seen a patient die of rheumatic pericarditis, the authors adding, "but then he is chiefly referring to adults and not to children." DeLiee and associates[59] observed that first attacks of rheumatic polyarthritis were less often accompanied by clinically evident carditis in adults than in children, and when carditis did occur it was much less likely to result in serious cardiac damage in the adult. In this connection it seems significant that idiopathic pericarditis is primarily a disease of adult life.[24] The average age in cases of idiopathic pericarditis was reported as thirty-five years.[61] In our series of twelve patients the average age was forty-five years, and only one patient was less than twenty years old.

It has been argued that absence of other rheumatic manifestations in non-specific pericarditis militates against a rheumatic etiology. Since it is known that rheumatic polyarthritis may occur without clinical evidence of cardiac damage, and vice versa, it should not be surprising if other exudative processes such as pericarditis and pleurisy were to occur as sole manifestations of the rheumatic infection. Libman and Garber reported on postmortem findings of pericarditis and Aschoff bodies in the myocardium without involvement of the endocardium.[62,63] Some observers have pointed out that acute pericarditis may antedate other signs of rheumatic fever, and that on occasion endocarditic manifestations are missing when rheumatic pericarditis, pleurisy or pneumonitis dominates the clinical picture.[3,51–53,56–58,66] Of great interest is the case of a youth, reported by Laubry,[38] who developed isolated pericarditis which promptly responded to salicylates. Two years later polyarthritis and endocarditis supervened. Moreover, it is erroneous to consider that myocarditis is absent in every instance of idiopathic pericarditis. The occurrence of dilatation of the heart, gallop rhythm, auricular flutter-fibrillation, and persistence of electrocardiographic changes and dyspnea long after cessation of the pericarditis may be regarded as evidence of involvement of the myocardium.[8,16,21,32,34] One of the patients of our series (Case 9) in the course of pericarditis and pleurisy developed congestive heart failure which outlasted all other clinical manifestations. There was no evidence of constrictive pericarditis.

A review of the literature reveals an unexpectedly high incidence of major or minor rheumatic manifestations in association with idiopathic pericarditis. In three instances a family history of rheumatic fever was elicited.[7,8,22] One patient gave a history of polyarthritis,[9] another of recurrent epistaxis.[7] A twenty-six year old woman had attacks of rheumatic fever at the age of eleven and fourteen years. Twelve years later she developed acute benign pericarditis following a sore throat.[18] A case of non-specific pericarditis has been reported with a history of repeated attacks of tonsillitis and of scarlet fever followed by "rheumatism."[1] Among eleven cases of non-specific pericarditis observed by Evans,[13] two patients had rheumatic valvular disease. Spear described five instances of fibrinous pericarditis which developed after thyroidectomy; in two of the cases old rheumatic heart disease was present.[17] Taubenhaus and Brams reported three cases of non-specific pericarditis;

one patient gave a history of chorea, another had "a fairly loud systolic murmur at the apex of the heart" that had persisted unchanged for years.[28] Cassio and Berconsky observed acute benign pericarditis and pleurisy in a forty-four year old woman who, at the age of twelve had scarlet fever and, at ages seventeen and twenty experienced "rheumatic pains" in both knees. Fever and pain of pericarditis were promptly abolished by pyramidon.[24] Mention has already been made of the case reported by Laubry in which isolated pericarditis was followed after two years by polyarthritis and endocarditis.[38] In the cases of idiopathic pericarditis observed by the writer rheumatic manifestations were noted in two-thirds of the patients. (Table 1.) Five patients gave a family history of rheumatic heart disease; in one instance the mother and sister also suffered from polyarthritis. One patient had frequent epistaxis in childhood. Two patients presented mild rheumatic valvular lesions.

Serologic tests in support of a rheumatic etiology were negative in most of the cases of idiopathic pericarditis, as well as in the postcommissurotomy syndrome. Only one-sixth of our series of idiopathic pericarditis had elevated antistreptolysin O titers, ranging from 333 to 1,250 units. (Table 1, Cases 1 and 11.) Levy and Patterson observed high antistreptolysin titers in three of sixteen cases of acute pericarditis in which serologic tests were made. In two of these patients cultures from the throat grew out hemolytic streptococcus. Absence of a high antistreptolysin titer is no evidence against rheumatic infection, since positive serologic responses are not obtained in from 10 to 20 per cent of the cases, especially in those with mild rheumatic infections.[64,65] Besides, negative serologic reactions are the rule in those instances in which rheumatic activity is precipitated by a non-specific agent.[44]

TREATMENT

Therapeutic effects have a significant bearing on the question of etiology. Sulfonamides, penicillin and streptomycin do not affect the course of idiopathic pericarditis.[2–4] Some writers observed a beneficial action of aureomycin or terramycin.[6,18,28] This was denied by others.[7,13] Cortisone causes dramatic improvement of idiopathic pericarditis.[7] Similar therapeutic results were obtained in the postcommissurotomy syndrome.

Salicylates given in large doses were reported to cause prompt relief of rheumatic pericarditis.[67] French authors successfully treated "primary" or "isolated" pericarditis and pleurisy with salicylates given in daily doses of 8 gm.[19–22,38] They concluded that those cases responding promptly to salicylates were of rheumatic origin. American investigators who tried salicylates or pyramidon in idiopathic pericarditis observed both failures[1,3,7] and beneficial effects.[24,68] Similar variations in the therapeutic effect of salicylates were observed in cases of rheumatic pericarditis.[46] Six patients of our series of idiopathic pericarditis were treated with salicylates or pyramidon. Improvement was slight in some instances, dramatic and convincing in others. Pyramidon seems to be more effective than aspirin. In general, therapeutic effects should be evaluated cautiously because an attack of idiopathic pericarditis may not last longer than a few days. The cases particularly suitable for critical evaluation of therapy are those which run either an unusually protracted course or in which severe pain is resistant to powerful analgesics. One of our patients (Table 1, Case 6) who suffered excruciating pain aggravated by breathing failed to respond to hypodermic administration of 100 mg. of dermerol. However, the pain was promptly relieved by 10 gr. of aspirin and the patient was even able to go to work when the same dose of aspirin was repeated every four hours. In this case the impression was gained that aspirin had a specific therapeutic action. The following very brief case report illustrates a dramatic effect of aspirin and pyramidon in an instance of pericarditis and pleurisy with unusually protracted course.

Case 11. R. G., a fifty-seven year old woman, who had diabetes, hypertension and marked left ventricular hypertrophy, developed dyspnea and swelling of the ankles for the first time at the age of fifty-seven, coincident with the occurrence of pericarditis and pleurisy Fever of irregular type was present. A single blood culture showed growth of Streptococcus viridans. There was no clinical evidence of bacterial endocarditis. Fever persisted for five weeks in spite of intensive treatment with antibiotics. Aspirin, which was given on the thirty-sixth hospital day, caused rapid fall of the temperature to normal. (Fig. 1.) Temporary withdrawal of aspirin was followed by return of fever, chest pain, pleural and pericardial effusion. Pyramidon was then substi-

tuted for aspirin which had caused deafness; it had an antipyretic effect like that of aspirin. The temperature remained normal under continuous treatment with pyramidon and the patient was comfortable but the sedimentation rate remained high and evidence of congestive heart failure was present for several weeks after other signs of pericarditis had disappeared.

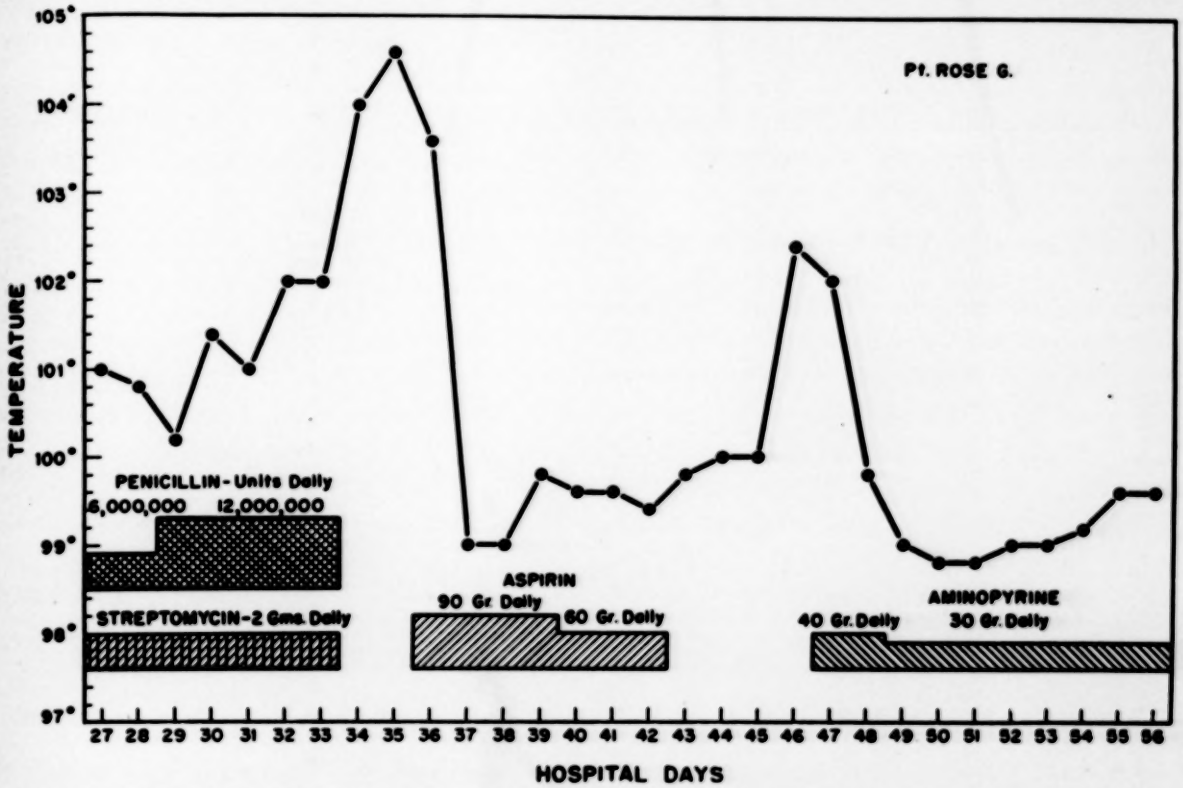

FIG. 1. Case II. The temperature chart shows the last part of a period of irregular fever of five weeks' duration. Between the twenty-seventh and thirty-third hospital day the temperature spiked during intensive antibiotic therapy and continued so after withdrawal of the antibiotics. On the thirty-sixth hospital day aspirin was given, which caused an abrupt fall of the temperature. Withdrawal of aspirin on the forty-second hospital day was followed at first by a gradual and then by a steep rise of the temperature curve. Aminopyrine, started on the forty-seventh hospital day, brought the temperature back to normal promptly.

In this case "idiopathic" pericarditis was diagnosed by exclusion. The family history suggested a rheumatic factor. The surprising therapeutic effect of salicylates and pyramidon seemed to be consistent with a rheumatic etiology of the serositis.

SUMMARY

Forty-two episodes of idiopathic pericarditis occurring in twelve patients were studied. The manifestations were compared with those observed in seventy-two attacks of the postcommissurotomy syndrome in twenty-four patients.

There is a striking resemblance between the clinical and laboratory features of idiopathic pericarditis and those of the postcommissurotomy syndrome. Both diseases include pericarditis, pleurisy and pneumonitis although the incidence of these components varies in the individual case. In some instances the occurrence of gallop rhythm, dilatation of the heart, transient auricular flutter-fibrillation and congestive heart failure suggests involvement of the myocardium. The outstanding clinical features are pain of the pleuropericardial type and fever. Both syndromes usually have a benign course and tend to relapse frequently.

There are compelling reasons for the belief that the postcommissurotomy syndrome is a manifestation of rheumatic activity. The same etiology is suggested for some cases of "idiopathic" pericarditis by the following facts: (1) Close resemblance of idiopathic pericarditis and the postcommissurotomy syndrome; (2) presence of major and minor rheumatic manifestations in a relatively large number of cases of

idiopathic pericarditis reported in the literature and in two-thirds of the cases observed by the writer; (3) salicylates and pyramidon sometimes have a beneficial, even dramatic effect in cases of idiopathic pericarditis; and (4) idiopathic pericarditis is predominantly a disease of the adult. Rheumatic fever in the adult is known to manifest itself often atypically, as a benign exudative process which may heal without residual heart disease.

The finding of pleurisy and/or pneumonitis aids in the differentiation of idiopathic pericarditis from an acute coronary attack.

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Treatment of Subacute Bacterial Endocarditis with Negative Blood Cultures

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Prior to the antibiotic era subacute bacterial endocarditis was, with rare exceptions, an inevitably fatal disease. Since the advent of the antibiotics their proper usage has resulted in a high percentage of complete cures. When the blood culture is positive and the offending organism can be isolated, it is a relatively simple matter to test the sensitivity of the organism to various bactericidal agents *in vitro*. The most efficient antibiotic is then chosen; it is administered in adequate quantity and for a sufficient period of time to kill all of the organisms in the blood stream, and presumably in the vegetations on the heart valves. That this is not always accomplished even in apparent clinical cures has been shown by many investigators. Cates and Christie[1] in a review of 442 patients treated in fourteen centers appointed by the Penicillin Trials Committee of the National Research Council state that, in supposedly cured patients who died from other causes, live organisms could be cultured from 30 per cent of cases in which the usual clinical criteria for the control of infections were established. Keefer[2] in his excellent review of the present day treatment of subacute bacterial endocarditis points out why difficulties are encountered during therapy in the effort to establish a bacteriologic cure. The vegetations from the heart valves consist of three layers: a central necrotic core of relatively acellular, fibrillar debris and two layers of bacterial colonies surrounding the central core. Both of these layers are covered by a delicate fibrillary acellular material resembling fibrin and platelets. It is difficult for leukocytes to penetrate this barrier. There is also indirect evidence that anti-infective agents have difficulty in diffusing through this wall.

Eagle et al.[3] present data which indicate that penicillin is most rapidly effective if the concentration at the focus of infection remains continuously in excess of that necessary to kill the particular organism at the maximum rate. Sensitivity tests do not determine the concentration of penicillin that kills the organism at the fastest possible rate but rather the concentration that prevents visible growth under the arbitrary conditions of the particular test. The most rapidly bactericidal concentration is usually three to ten times this barely inhibitory concentration. Furthermore, since about half the circulating penicillin is believed to be bound to serum protein, the concentration of antibiotic available for diffusion into tissue fluids may be only half that present in the serum. On these two grounds alone the serum concentration should be five to twenty times the sensitivity level of the organism. If in addition, as Keefer observes, the diffusion of penicillin into the vegetations is limited by histopathologic changes, an even larger multiple of the inhibitory concentration must be provided in the serum to assure the presence of the maximally effective concentration at the focus of infection. For practical purposes a serum concentration ten times the sensitivity level will suffice. However, the schedule of therapy should be such as to provide this level continuously in order to prevent the emergence of resistant strains of the organism. If the patient is started and continued on inadequate dosage, the chance of recovery may be jeopardized or treatment prolonged unnecessarily. Orgain and Donegan[4] showed that in one of their patients the sensitivity of the organism changed from 0.25 units of penicillin per cc. to 24 units per cc. in twenty-eight weeks even though the initial daily dosage was begun at 1,500,000 units per day and was increased in a few days to 5,000,000 units per day. In another cured case the organism increased its resistance from 0.001 to 1.0 unit of penicillin per cc. in four weeks.

The total duration of the treatment is just as important a consideration in obtaining a bacteriologic cure as is the total daily dose of the antibiotic. Reports have appeared in the literature relating to courses of treatment lasting from two to three weeks. Geraci[5] reporting from the Mayo Clinic cites fifteen patients in whom endocarditis was caused by penicillin-sensitive streptococci, when combined short-term therapy with penicillin and dihydrostreptomycin was used. The daily dose of penicillin was 1,200,000 to 2,400,000 units and 1.2 to 2.4 gm. of dihydrostreptomycin daily. The course of treatment lasted fourteen to twenty days. On the other hand, Orgain and Donegan[4] advise that treatment should last at least four to six weeks initially and longer if a relapse occurs. Littman and Schaaf[3] treated their patients for periods ranging from thirty to sixty days.

It has been our practice in all suspected cases of subacute bacterial endocarditis to draw blood for culture at least twice on the day of admission and daily thereafter for three days before definitive therapy is started. As soon as a positive culture is obtained, the sensitivity of the organism against the various antibiotics is tested even before it is identified. If the organism is entirely resistant to penicillin, the antibiotic to which the organism is most sensitive is administered in adequate dosage by the best route available for a period of at least five weeks. If it is found to be penicillin-sensitive, we give intravenously over a twenty-four-hour period 10,000,000 units of penicillin dissolved in 1 L. of 5 per cent glucose in water in which 10 mg. of heparin are added to prevent thrombosis at the site of venipuncture. Where veins are difficult to puncture a cut down is performed, a vein isolated and a polyethylene catheter inserted. It has thus been possible in all of our recent cases to continue intravenous therapy for a minimum of five weeks. Benemid® has been given simultaneously in some instances to enhance the penicillin blood level. Occasionally streptomycin or dihydrostreptomycin in divided doses of 2 to 3 gm. daily by the intramuscular route has been added. By this means we have been able to effect a bacteriologic cure in every one of twelve such cases. Within forty-eight to seventy-two hours after initiation of treatment the temperature falls to normal and the blood cultures become negative. At the end of a week there is dramatic improvement in the patient's subjective symptoms. Weekly blood cultures during the course of treatment continue to be normal. Embolic phenomena may occur even after sterilization of the infection; these, as well as phlebitis at the site of venipuncture, may occasionally cause a slight rise in the temperature. No serious untoward symptoms have occurred with this dosage. The patient need not be confined to bed continuously. A wheelchair is fitted with an extension from which to hang the infusion bottle and, after the temperature has been normal for a few days, the patients are permitted to wheel themselves about the room or corridor. Some patients are given bathroom privileges. The bottle is carried and hung by the patient on a hook on the bathroom wall while using the toilet. Among those patients in whom the organism is more resistant, Geraci[5] and the author and his coworkers[7] have continued treatment with massive doses of antibiotics for from six to eight weeks.

The meticulous care one must give to the details of dosage and duration of treatment is of even greater importance when therapy is undertaken in cases in which positive blood cultures cannot be obtained. The difficulties in establishing a diagnosis are manifold. Friedberg[9] and Glotzer,[10] in reviewing autopsied cases in which a clinical diagnosis had not been made during life, list the reasons for such failures, among which was the absence of positive blood cultures. This led to abstinence from or long delay in initiating treatment, a factor of great importance in causing a fatal outcome. The physician must quickly decide what drug or drugs should be chosen, in what dosage they should be used, what route of administration should be employed, and for how long antibiotics should be continued.

Friedberg[8] points out that in 95 per cent of the cases of subacute bacterial endocarditis the causative organism is a non-hemolytic streptococcus and further that, of these, Streptococcus viridans is the cause in about 80 per cent. Although the great majority of bacteremias due to this organism can be controlled by doses of 1,000,000 units or less of penicillin per day, there is the possibility that one is dealing with an organism of higher resistance. It therefore seems to me that if the patients were treated as if there were a resistant organism, the chances of obtaining a bacteriologic cure would be enhanced, and no harm would be done if the organism were of the usual sensitive type. Streptomycin and dihydrostreptomycin do not diminish the effectiveness of penicillin and may even enhance it.

Also, they may be effective against bacteria which are penicillin-resistant. We therefore start treatment with 10,000,000 units of penicillin daily by the continuous intravenous route, and give 2 to 3 gm. of streptomycin or dihydrostreptomycin in divided doses daily by the intramuscular route. If these are therapeutically effective, the temperature should become normal in from forty-eight to seventy-two hours. Should this not occur, the dose of penicillin may be doubled and benemid may or may not be added. If within another twenty-four hours the temperature has not become normal or appreciably lower, both drugs are discontinued and one or a combination of the other antibiotics is started. If penicillin and streptomycin are partially but not completely effective, they are continued and one or another antibiotic and at times a triple sulfonamide is added. When the effective drug or combination of drugs is found, treatment should be continued in the maximum dosage for a period of at least five weeks unless severe reactions occur to contraindicate their continued use. Such toxic effects as drug rash, leukocytosis, phlebitis at the site of injection, etc., should be treated by appropriate means but the life-saving course of treatment should be continued if possible.

The following cases illustrate the use of such a regimen in subacute bacterial endocarditis when positive blood cultures cannot be obtained. All the patients described remained well for periods ranging from four months to two years.

CASE REPORTS

CASE I. M. S., a fourteen year old white male, was admitted to Beth-El Hospital on December 9, 1951, complaining of malaise and fever of three weeks' duration. There were some mild gastrointestinal disturbances at the onset. The temperature ranged from normal to 103°F. The family physician stated that a cardiac murmur was heard on previous examinations but no importance was attached to it. The patient appeared febrile but was in no acute distress. There were prominent lymph follicles in the pharynx and a few small nodes were palpable in the posterior cervical chains. The heart showed sinus tachycardia and a grade I systolic murmur was audible over the precordium with greatest intensity at the mitral area. No thrills were palpable. No petechiae were noted. The blood hemoglobin was 68 per cent, red cell count 3,740,000 per cu. mm., white cell count 8,000 per cu. mm., with a normal differential count, and the platelet count was normal. Sedimentation rate was 36 mm. per hour (Wintrobe). The urine showed rare red and white blood cells. Blood chemical examinations including urea nitrogen, serum proteins, bilirubin, cephalin flocculation, thymol turbidity, cholesterol and esters and the Mazzini test gave normal results. Serologic tests for infectious mononucleosis, typhoid fever, paratyphoid fever, brucellosis and cold agglutinins were negative. An L. E. preparation was negative. On December 13th the Weil-Felix reaction was positive in dilutions up to 1:80. On December 18th it was positive in dilutions up to 1:160. On December 26th it was positive in a dilution of 1:320. Specimens of blood submitted to the Board of Health on December 17th and 26th were found to be anticomplementary for rickettsialpox, epidemic typhus, endemic typhus and Rocky Mountain spotted fever. Eight blood cultures taken before antibiotic therapy was started and cultured aerobically and anaerobically for five weeks were negative. Electrocardiograms, x-rays of lungs, kidneys and abdomen were negative.

The temperature shortly after admission rose to 105°F. Large doses of salicylates were without effect. On December 13th petechiae were noted in the conjunctival sac and on the soft palate. Penicillin given in dosage up to 1,000,000 units daily intramuscularly, first in conjunction with chloromycetin® and then terramycin® up to 2 gm. orally, and later 1 gm. of streptomycin intramuscularly, caused a gradual fall in temperature to 100°F. where it remained until December 25th when it spiked to 103.6°F. On the following day the patient was seized with severe left-sided abdominal pain. Conjunctival petechiae and Osler nodes were noted. For the first time a change in the cardiac findings was observed. A loud blowing grade IV systolic murmur was audible over the entire precordium. The urine showed numerous red blood cells. The white blood cell count was elevated to 44,000 per cu. mm. with a marked shift to the left.

On December 27th penicillin was started by continuous intravenous drip in a dosage of 10,000,000 units daily, in conjunction with 1 gm. of streptomycin intramuscularly and 1 gm. of terramycin orally. When the temperature did not reach normal forty-eight hours later, 6 gm. of a triple sulfonamide preparation were added

daily in divided dosage. Twenty-four hours later the temperature returned to normal. Generalized pruritus was readily controlled by pyribenzamine.® The temperature remained normal with occasional rises to 100°F. On January 21, 1952, all therapy was discontinued. The following day the patient complained of a sore throat and congested nose. Physical findings of an upper respiratory infection were present. The temperature rose to 102°F. The previous therapy was reinstituted. After forty-eight hours the temperature returned to normal. Therapy was continued until January 27th. The temperature remained normal until his discharge on February 1st. The white blood cells gradually fell to a normal count of 9,600 per cu. mm.

On February 13th, while the patient was ambulant at home, he was seized with sudden severe pain behind the right knee. The right foot became cold and felt numb. There was a rise in temperature to 100.6°F. Examination disclosed absence of the popliteal, posterior tibial and dorsalis pedis pulses. The right foot was cooler and paler than the left. No oscillometric pulsations could be obtained below the right knee. Many red blood cells were found in the urine at this time. A diagnosis was made of embolic arterial occlusion of the right popliteal artery and embolization of the kidneys. The dorsum of the foot developed mottled cyanosis but after a few days the color and temperature of the foot became normal and all abnormal sensations disappeared. To date the patient has remained perfectly well with no complaints referable to the arterial circulation although the main artery remains totally occluded. The cardiac murmur has diminished in intensity so that it is heard with difficulty even after exercise.

Comment. This young boy who had unexplained fever, an insignificant murmur and no signs of clinical subacute bacterial endocarditis subsequently developed all the manifestations of this disease. At no time was a positive blood culture obtained. The rising titer of the Weil-Felix reaction can be explained only as a nonspecific, anamnestic response triggered by the organism which caused the endocarditis. Fairly large dosage of the antibiotics caused only partial and temporary fall in temperature. Not until massive doses of penicillin were given by continuous intravenous drip, together with streptomycin, terramycin and the sulfonamides, was there complete subsidence of fever and a satisfactory clinical response. Arterial occlusion after discharge was probably caused by a sterile embolus originating in the heart valves. The fact that the patient has remained completely well for two years and that the intensity of the murmur has diminished until it is almost inaudible indicates that an anatomic as well as a clinical and bacteriologic cure has been obtained.

Case II. S. W., a thirty-one year old white married woman, was admitted to Beth-El Hospital on September 11, 1953, with complaints of headache and intermittent fever of four weeks' duration. She had been treated at home with aureomycin and sulfonamides without effect. She had knowledge of a cardiac murmur since the age of twelve but gave no history suggestive of rheumatic fever. Examination of the heart disclosed tachycardia and a loud grade IV systolic murmur over the entire precordium with maximum intensity at the pulmonic area. No thrills were palpable. P_2 was accentuated. The blood pressure was 130/70. The spleen was not palpable but Traube's space was obliterated upon percussion suggesting splenomegaly. The urinalysis was negative. The blood hemoglobin was 67 per cent, the red cell count 3,500,000 per cu. mm. and the white cell count 5,000 per cu. mm. with a normal differential count. The sedimentation rate was 27 mm. per hour (Wintrobe). Blood chemical analyses including glucose, urea nitrogen, serum proteins, thymol turbidity, cholesterol and esters were normal. The enteric, cold and heterophil agglutination tests were negative. Stool and urine cultures were negative. Six blood cultures obtained during the first four days failed to grow out organisms for a period of six weeks. An L. E. preparation was negative. X-ray of the chest showed the heart to be of normal proportions. The lungs were negative. An esophagram was negative. The electrocardiogram was normal except for sinus tachycardia. The temperature upon admission was 103°F. and ranged between this level and 99°F. until September 16th. On this day the patient complained of abdominal pain, suffered a severe shaking chill, developed a picture of mild peripheral circulatory failure and a fall in blood pressure to 100/70 and in temperature to 97.4°F. With shock treatment the blood pressure rose to the patient's normal level and the temperature reached its previous peak of 102.4°F. A continuous intravenous drip of 10,000,000 units of penicillin daily was immediately started and 2 gm. of streptomycin were given daily intramuscularly in divided doses.

The temperature gradually fell within thirty-six hours but never reached the normal level, ranging between 99° and 100.8°F. daily. After one week the temperature began to climb and reached 103°F. Penicillin and streptomycin were discontinued on September 23rd and 3 gm. of oral terramycin was started daily in divided dosage. The temperature fell to normal within twelve hours where it remained for the rest of her hospital stay. On September 29th the dose was reduced to 2 gm. daily. She was discharged October 1st and continued to take this dose at home for four weeks. This dose was then gradually reduced over a period of a week and finally discontinued. The patient has remained well to date. The intensity of the murmur has diminished.

Comment. This thirty-one year old woman, known to have a cardiac murmur for nineteen years, developed a febrile illness lasting one month before she was hospitalized. All other causes of fever were ruled out. In the presence of an accentuated cardiac murmur, moderate anemia and enlarged spleen, a diagnosis of subacute bacterial endocarditis was established despite the many negative blood cultures. Penicillin in massive doses by the intravenous route and streptomycin were ineffective. Terramycin given orally in large dosage caused a rapid fall in temperature and ultimately a complete clinical cure.

CASE III. B. M., a forty-five year old white married man, was admitted to Beth-El Hospital on August 25, 1953, complaining of fever, pain in the left calf and a painful, red, swollen area on the inner aspect of the right ankle. He had been ill since January, 1953, with constant weakness and repeated bouts of fever. He had knowledge of the presence of a cardiac murmur for at least two years. He was previously admitted to this hospital in July, 1953, at which time a comprehensive study, including many blood cultures, failed to reveal the cause of his complaints. Treatment with many antibiotics in ordinary dosage and salicylates failed to ameliorate his symptoms. He signed a release from the hospital two weeks after admission, the discharge diagnosis being fever of undetermined origin. His symptoms continued unabated. Shortly before admission there was a five-day episode of pain and swelling over the right parotid area.

Physical examination revealed a pale, acutely and chronically ill patient. The temperature was 102°F. The neck vessels were pulsating forcefully and rapidly. The heart showed left ventricular enlargement. Loud systolic and diastolic murmurs were audible at the aortic area. A Corrigan pulse, pistol-shot femoral artery pulsations and a blood pressure of 140/0 confirmed the diagnosis of aortic regurgitation. The spleen was not palpable but appeared enlarged by percussion. The left leg showed evidence of thrombophlebitis. A tender, erythematous area was present on the inner aspect of the right ankle. The fingers showed slight clubbing.

Urinalysis showed a trace of albumin, the sediment containing a few red and white blood cells. The specific gravity was 1.015. A Fishberg concentration test showed a fixation of the specific gravity at 1.016. The blood hemoglobin was 10.5 gm. per cent, the white cell count 6,700 per cu. mm. with a normal differential count. The sedimentation rate was 20 mm. per hour (Wintrobe). The Mazzini test was negative. The serum proteins were 8.2 gm. per cent, 4.4 gm. albumin and 3.8 gm. globulin. A thymol turbidity test of 19 units and cephalin flocculation test of 4 plus were obtained. Blood glucose, urea nitrogen, Van den Bergh, alkaline phosphatase, cholesterol and esters were normal. A bromsulphalein test showed only 1 per cent retention of dye at the end of forty-five minutes. An L. E. preparation was negative. Enteric, heterophil and cold agglutination tests were negative, as were stool and urine cultures. Ten blood cultures, four taken in one 24-hour period and grown for six weeks under aerobic and anaerobic conditions, were negative. X-ray of the chest showed an enlarged heart with configuration consistent with aortic valve disease. X-rays of the teeth and sinuses were negative. The electrocardiogram showed left axis deviation without other significant abnormalities. Biopsy of the lesion on the right ankle showed no significant findings. The spleen was found to be palpable on August 31st. The left parotid area became swollen and exquisitely tender on September 3rd and the patient had difficulty opening his mouth. X-ray of the temporomandibular joint was negative. Because of the presence of fungus infection of the toes and a questionable skin reaction to penicillin previously given, an intradermal sensitivity test was performed which proved negative.

On September 4th therapy was started with 10,000,000 units of penicillin by continuous intravenous drip and 3 gm. of streptomycin daily

in divided doses. The temperature, which was 102°F., receded to normal in forty-eight hours, spiked to 103°F. on the third day, returned to normal the same day and remained practically normal for the remaining five weeks of treatment. An occasional rise to 100°F. was ascribed to phlebitis at the venipuncture site. On September 24th there was severe abdominal pain and a rise in temperature to 100.2°F. This was ascribed to mesenteric embolization. The pain subsided after two days. The patient's general appearance improved, he became stronger and his appetite increased markedly. The hemoglobin rose to 11.8 gm. per cent. The spleen receded. The abnormal blood chemical findings returned to normal. He was discharged on October 11, 1953. To date the temperature has remained normal.

Comment. This forty-five year old man with a known cardiac murmur developed subacute bacterial endocarditis at least eight months before intensive treatment with intravenous penicillin and intramuscular streptomycin was instituted. The urinary findings were suggestive of chronic glomerulonephritis. Since his discharge slight dyspnea and a hacking cough have developed which have responded well to a salt-free diet, oral mercurial diuretics and digitalis. Although the bacteremia has been cured, the onset of symptoms of early left ventricular failure and chronic glomerulonephritis indicates the serious prognosis in this case. Had therapy been started sooner the severe valvular deformities, marked regurgitation and congestive heart failure may not have occurred so soon after bacteriologic cure.

SUMMARY

1. The treatment of subacute bacterial endocarditis is discussed and the need for early, intensive and prolonged treatment stressed.

2. The management of cases with negative blood cultures is outlined and three illustrative cases are cited.

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Euthyroid Patients with Early Eye Signs of Graves' Disease*

Their Responses to L-*Triiodothyronine and Thyrotropin*

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OCCASIONALLY, the eye signs of Graves' disease appear before there is other evidence of hyperthyroidism. Little is known about the status of the thyroid in these patients but it has been generally assumed that the gland has not yet been involved by the disease. A tool to investigate the functional status of the gland, which would be particularly appropriate to test this assumption, has been provided by recent work.[1,2] The present report describes the clinical characteristics of a group of ten such euthyroid patients with the early eye signs of Graves' disease (Tables I, II and III), and the results obtained with these tests of function. (Tables IV and V.)

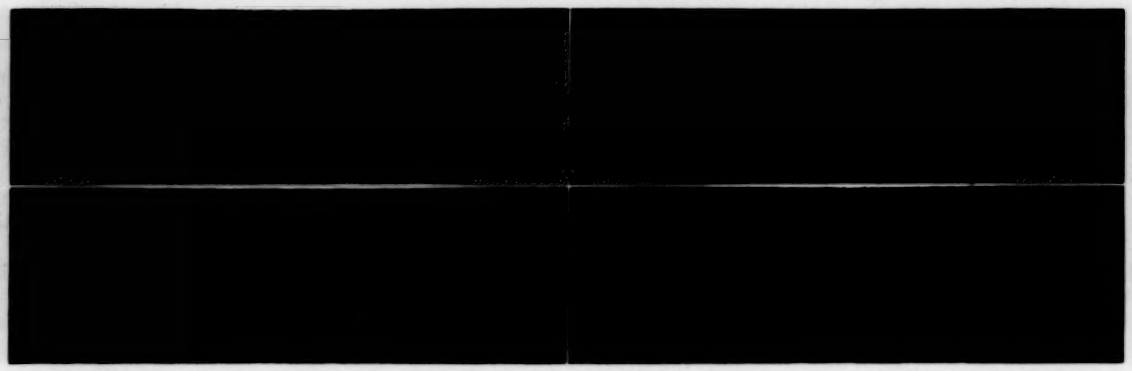

FIG. 1. The eyes of four patients of the present series showing the characteristic features of the early changes of Graves' disease despite the euthyroid status. Onset was noted between three and four months prior to the photographs. Patients R. A., A. M., M. E. and D. S.

It was demonstrated in the previous studies that the responses to L-triiodothyronine and thyrotropin of patients with overt hyperthyroidism were different from those of euthyroid control subjects. The administration of thyroid or triiodothyronine, even in toxic amounts, did not depress the uptake of I-131 by the thyroid of patients with Graves' disease whereas they markedly lowered uptake in patients without thyroid disease or in patients with non-toxic diffuse goiter. Thyrotropin in turn did not increase I-131 uptake in Graves' disease although the level of serum precipitable iodine (SPI) was elevated; in normal subjects both uptake and serum levels were increased by administration of the hormone.

A study of the effects of these agents in the euthyroid patient with eye signs was made to study several questions: (1) whether these patients really have Graves' disease; (2) whether euthyroidism can be maintained when the pituitary thyroid balance is interfered with and (3) whether Graves' disease is caused by hyperpituitarism or is mediated by mechanisms apart from the anterior pituitary.

CLINICAL PICTURE

All ten patients were seen in the past year because of the eye disorder. (Fig. 1.) There were

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nine women and one man; ages varied from twenty-four to sixty-three years. The eye changes had been first observed within two to eight months of the time of the initial visit and were noted to be unilateral in five and bilateral in five. Diplopia was complained of by three patients. Apart from the presenting complaint, other symptoms were minimal. (Table I.) Undue nervousness was described by six patients but had always been present in three of the six. The maximum weight loss recorded was 8 pounds and in this patient a reducing diet had been given; only two others lost a few pounds. Three patients had had tremor, reported as from two to many years' duration. Three patients had observed the recent onset of palpitation and two of fatigue. The system review was otherwise strikingly negative.

TABLE I
SYMPTOMS PRESENTED BY TEN EUTHYROID PATIENTS WITH EARLY EYE SIGNS OF GRAVES' DISEASE

Symptom	No. Patients
Eye involvement:	
Unilateral	5
Bilateral	5
Diplopia	3
Duration	2–8 mo.
Nervousness	6 (3 always)
Tremor	3 (2 yr. to 6 yr.)
Palpitation	3
Weight loss	3 (1 on diet)
Heat intolerance	2 (1 always)
Fatigue	2
Diarrhea	1
Change in menses	0
Noticeable gland	0
Gland weight (approximate):	
25 gm. or less	4
25–35 gm.	6

On physical examination, apart from widening of the fissures and a limited degree of proptosis or, in the patients with diplopia, of motion of the globes, the thyroid represented the only feature of note. It was palpable in six of the ten, in which instances it was minimally and diffusely enlarged. (Table I.) There was no characteristic tremor; the palms were moist and the pulse rate was slightly elevated in about half of the patients.

Values for the basal metabolic rate (Table II) ranged from −21 per cent to +10 per cent, averaging −2 per cent; fasting cholesterol levels were between 145 and 210 mg. per cent; chemical SPI values were less than 7.5 μgm. per cent in all but three instances averaging 7.2 μgm. per cent (normal for the method in this laboratory is 3.5 to 7.5 μgm. per cent; serum precipitable I-131* (SPI-131) values at seventy-two hours after the I-131 was given were normal in four of the six patients tested, namely, less than 0.3 per cent, and were increased in the other two.

Course. Two patients showed signs of pro-

* Serum precipitable I-131 measurements were made by a modification of the method of Silver and co-workers[3] which made it possible to determine the SPI-131 content with the original 15 μc. dose of I-131 used for the uptake determination.

TABLE II
LABORATORY VALUES AND HERTEL EXOPHTHALMOMETER MEASUREMENTS

Patient	BMR (%)	Cholesterol (mg. %)	SPI (μgm. %)	24-hr. I-131 Uptake (%)	72-hr. SPI-131 (%)	Hertel Exophthalmometer Reading (mm.)	
						O. D.	O. S.
D. S.	−3	199	7.0	40	<0.3	17	18
M. E.	−15	231	7.0	27	<0.3	22½	22
K. W.	−21	...	5.2	29	<0.3	17	22
R. K.	+7	...	9.7	68	1.4	20	17½
S. N.	+7	220	6.6	47	...	14	16
R. H.	+10	145	11.3	39	...	26	23
A. M.	+3	260	8.1	44	0.4	23	22
T. M.	−6	180	4.5	29	...	18½	25½
R. A.	−1	...	5.3	32	<0.3	20	18
P. E.	±0	209	7.3	10	...	21½	22½

gression of disease during the year of observation, the other eight remained unchanged by all criteria. One of those with progression developed edema about the lids and widening of the left ocular fissure, as well as the right, nine months after onset. The second patient with advancing disease became overtly thyrotoxic three months after the first visit. She was given I-131 therapeutically with improvement in the eyes and gain in weight and well being. One of the patients not considered toxic was given propylthiouracil by another physician and gained 11 pounds in the two months before she was lost to follow-up. Another received sodium iodide intermittently for six months without demonstrable result.

TABLE III
DURATION AND RESULTS OF FOLLOW-UP OBSERVATIONS

Patient	Duration	Status at Last Visit
D. S.	1 yr.	O. S. involved after 9 months; euthyroid
M. E.	10 mo.	Unchanged
K. W.	3 mo.	Cerebral accident
R. K.	1 yr.	Hyperthyroid after 3 months and better after I-131 therapy
S. N.	2 mo.	11 lb. gain after propylthiouracil
R. H.	2 yr.	Unchanged; still unresponsive to triiodothyronine
A. M.	6 mo.	"Well"
T. M.	8 mo.	Unchanged
R. A.	6 mo.	Unchanged
P. E.	6 mo.	Unchanged

Effects of L-*Triiodothyronine.* The effects of L-triiodothyronine administration upon twenty-four-hour I-131 uptake by the thyroid in the patients of this group are listed in Table IV. After an initial determination of uptake at twenty-four hours, made with a 15 μc. test dose of I-131, all patients were given L-triiodothyronine by mouth in doses ranging from 0.07 or 0.75 mg.* to 1 mg. daily, as the sodium salt, for eight days. On the morning of the eighth day the radioactivity remaining in the thyroid was measured, a second 15 μc. dose of I-131 was administered and the twenty-four-hour uptake again determined.

The absence of decrease in uptake by the thyroid in the euthyroid patients with eye signs of Graves' disease is in striking contrast to the marked decrease in uptake shown by thirty euthyroid control subjects. (Table IV.) Only one patient in the control group receiving 75 μgm. L-triiodothyronine daily had a final uptake value higher than 20 per cent and this dropped to 1 per cent upon the administration of 0.15 mg. of the drug for eight days, whereas all but one final value was 20 per cent or more with the 75 μmg. dose in the patient group, and this value was initially 10 per cent.

TABLE IV
EFFECT OF TRIIODOTHYRONINE UPON TWENTY-FOUR-HOUR I-131 UPTAKE BY THE THYROID

Patient	Triiodothyronine daily dose mg.	I-131 Uptake (%)	
		Before	After
D. S.	0.07	40	49
	1.0	49	30
K. W.	0.07	29	33
	1.0	33	20
R. K.	0.07	68	64
R. H.	0.07	39	48
	0.5	38	54
A. M.	0.07	44	45
T. M.	0.07	29	21
	0.5	24	35
R. A.	0.075	32	20
	0.150	20	17
P. E.	0.07	10	10
	0.5	10	3
S. M.	120.0 (thyroid)	47	46
M. E.	180.0 (thyroid)	27	24
		Average 34	32
Controls (30 subjects)	0.075	Average 35 Range 12–64	11 1–36*

* One patient only with uptake in excess of 20 per cent; this fell to 1 per cent with 0.15 mg. triiodothyronine daily.

The effects of doses of L-triiodothyronine up to 1 mg. daily upon the patients with eye signs only are also shown in Table IV. A limited decrease in uptake occurred in the two patients receiving 1 mg. daily.

Effects of Thyrotropin. The responses to thyrotropin in the euthyroid patients with early eye signs of Graves' disease are shown in Table V. Although there was a slight increase in

* The L-triiodothyronine content of the pills provided through the courtesy of Dr. A. Heming of Smith, Kline & French Labs. was changed from 35 μgm. each to 25 μgm. each during the study. L-triiodothyronine in the human is approximately four times as active as L-thyroxine and the 75 μgm. amount used is roughly equivalent to thyroid 0.12 gm.

average uptake of I-131 by the thyroid, the amount was negligible in five of the eight patients tested. On the other hand, a brisk increase in SPI level followed thyrotropin administration in all eight patients.

Thyrotropin (Armour) was used and was

TABLE V

EFFECT OF THYROTROPIN ON TWENTY-FOUR HOUR I-131 UPTAKE BY THE THYROID AND ON SERUM PRECIPITABLE IODINE VALUES

Patient	SPI (μgm. %)		I-131 Uptake (%)	
	Before	After	Before	After
P. E.	6.5	12.5	10	18
R. H.	6.9	14.0	54	30
A. M.	7.9	11.9	45	48
D. S.	7.1	9.2	33	58
R. W.	6.0	10.7	33	58
T. E.	9.5	16.8	49	53
T. M.	4.5	8.8	35	48
R. A.	5.3	7.1	32	30
Average	6.7	11.4	36	43

administered in doses of 10 units (30 mg.) daily for three days, given intramuscularly. A diagnostic dose of 15 μc. I-131 was given orally on the third day and uptake was determined twenty-four hours later. Blood for determination of SPI was obtained on the third or fourth day after the first thyrotropin injection, as well as before treatment.

COMMENTS

It is evident that at least seven of the ten patients with early eye changes of Graves' disease in this series were euthyroid by every criterion available. The other three were euthyroid by all criteria but the SPI, the levels of which were high; however, about 3 to 5 per cent of SPI values in our laboratory are in excess of 8 μgm. per cent in subjects with no known thyroid disease. Despite the lack of evidence of thyroid disease in the present ten patients, they showed the typical responses of active disease when triiodothyronine and thyrotropin were exhibited. It thus appears that the euthyroid patients under discussion have Graves' disease despite their euthyroid status, and that the thyroid is involved by the pathologic mechanisms responsible for that disorder.

In the healthy subject, it is recognized that pituitary activity is markedly suppressed when an excess of thyroid hormone is introduced into the circulation.[4] As a result, thyrotropin is not released and thyroid activity declines sharply as evidenced by a decline in I-131 uptake. The resultant decrease in level of circulating thyroid hormone releases the pituitary from inhibition, thyrotropin is liberated and the cycle repeats itself.

This delicate interplay is no longer operative in Graves' disease[1,2] or in the patients with early eye changes presently under discussion, and the mechanisms by which a normal circulating level of thyroid hormone is maintained in the face of this disruption of the pituitary-thyroid relation become of interest. Because of the disruption of the normal relations, and the abnormal responses of these patients to thyrotropin, together with other reasons stated elsewhere,[5] the author has concluded that Graves' disease is not caused by hyperpituitarism but is mediated by mechanisms apart from that gland.[5,6]

It is possible that the patients described herein may have had active Graves' disease in abortive form and undergone a spontaneous remission by the time they were first seen. This seems improbable in view of the brief history of disease. It is also possible that these patients do not have Graves' disease, since only one has become overtly hyperthyroid. Clinically, however, this seems unlikely, too, in view of the enlargement of the thyroid found in some of the patients, the uniformly disordered functional reactions of the gland and the fact that two other such patients not included in the series developed classic severe Graves' disease one to two years after onset of the eye complications.

As a by-product of these and earlier studies, the use of triiodothyronine and the twenty-four-hour uptake method as a test for hyperthyroidism has been investigated.[7] Greer has recently reported on the use of desiccated thyroid for the same purpose.[8] No twenty-four-hour I-131 uptake by the thyroid was found in our series to exceed 20 per cent following administration of triiodothyronine daily for a week. In patients with toxic goiter, however, no uptake following triiodothyronine administration was found to be less than 35 per cent. A few patients with nontoxic nodular goiter failed to respond to triiodothyronine. Radioautographs of the thyroids of these latter obtained at later operation re-

vealed the nodules to be functionally active. Patients in sustained remission from Graves' disease with residual eye changes responded to triiodothyronine like normal subjects.

SUMMARY

1. Ten euthyroid patients with the early eye signs of Graves' disease have been described.

2. These patients behave functionally in response to triiodothyronine and thyrotropin like patients with overt Graves' disease. It is concluded that these patients do, in fact, have Graves' disease.

3. It is demonstrated that the normal pituitary-thyroid relation is disrupted in these patients and that euthyroidism can be maintained despite this disruption. The implications of these observations in respect to the pathogenesis of Graves' disease are mentioned.

4. Triiodothyronine and the twenty-four-hour uptake method provide a new and highly reliable test of thyroid function.

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Relation between Serum and Cerebrospinal Fluid Electrolytes under Normal and Abnormal Conditions*

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CEREBROSPINAL fluid electrolytes have been studied thoroughly in the normal organism but incompletely in various disease states. Alteration of the concentration of cerebrospinal fluid electrolytes is followed by profound changes in the body as a whole.[1–10] The question arises whether such changes occur in certain clinical states and, if present, whether they affect the course of the disease. The consideration of alterations in cerebrospinal fluid electrolytes involves the problem of the relationship between serum electrolytes and electrolytes in the cerebrospinal fluid and the mechanism of cerebrospinal fluid formation.[20]

The purpose of this study was to investigate cerebrospinal fluid electrolytes in (1) normal human subjects, (2) patients with disease of the central nervous system, (3) patients with tissue and serum electrolyte imbalance, and (4) in animals in which various electrolyte disturbances were experimentally produced.

METHODS AND MATERIALS

Studies in Human Subjects. Serum and cerebrospinal electrolytes including sodium, potassium and pH were determined in twenty normal subjects and in fifty patients with various clinical abnormalities. The cerebrospinal fluid control samples in normal human subjects were obtained prior to the induction of spinal anesthesia in patients who were carefully screened for any clinical abnormality that might even remotely affect the cerebrospinal electrolytes. These patients had minor ailments requiring elective surgery, e.g., anal fistulectomy, hemorrhoidectomy and herniorrhaphy. All patients received routine preoperative medication consisting of the customary doses of barbiturates and/or opiates and atropine. The age range of these patients was twenty-three to sixty-three years; nine were males, eleven females.

The various clinical abnormalities studied are listed in Tables I and III. Patients belonging to these groups were approximately of the same sex and age distribution as the normal patients. The cerebrospinal fluid was obtained from these patients as soon as the clinical diagnosis was established and usually before specific treatment was started. The diagnosis of acute encephalomalacia was established on the basis of typical clinical findings, including hemiplegia, often stupor and aphasia, and a clear cerebrospinal fluid. A diagnosis of cerebral hemorrhage was made only in the presence of a grossly bloody cerebrospinal fluid, and was often confirmed by necropsy. Aneurysms of the cerebral vessels were demonstrated by an angiogram in those patients who recovered from the acute hemorrhagic episode. The diagnosis of tuberculous meningitis was confirmed by positive cultures of mycobacterium tuberculosis. Patients diagnosed as hypertensive encephalopathy in this series presented the following clinical manifestations: malignant progressive form of hypertension with periods of mental aberration, elevated cerebrospinal fluid pressure and a grade IV hypertensive retinopathy.

Prior to use all syringes, test tubes, syringe caps and needles were washed with detergent and water, rinsed with ether followed by distilled water and then autoclaved. Five ml. of cerebrospinal fluid were collected directly from the spinal needle into a Luer-Lok syringe, special care being used to prevent exposure to air. The syringe was capped immediately after withdrawal of cerebrospinal fluid and then

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packed in ice. Blood specimens were taken immediately thereafter, usually from one of the antecubital veins. A 5 ml. clotted specimen for serum potassium and sodium and a 5 ml. heparinized specimen for pH determination were obtained. Great care was likewise used here to prevent contact of the blood with air. The syringes were then placed in a beaker of cracked ice; all the specimens were immediately taken to the laboratory for analysis.

Analyses were made on the cerebrospinal fluid and hemolysis-free serum. For sodium and potassium determination, 1 ml. of each sample was used. Four ml. of 10 per cent trichloroacetic acid was added and the whole diluted to 10 ml. After standing ten minutes the solution was centrifuged and the supernatant fluid poured off. This (1–10 dilution of sample) was analyzed for potassium using the Beckman spectrophotometer, Model DU with flame attachment.[21] The 1–10 dilution of the sample was further diluted 1–20 and this 1–200 solution of the sample was analyzed photometrically for sodium. The samples were compared against standards containing potassium, sodium, and trichloroacetic acid in approximately the same amounts as found in the unknown. The same set of standards was used for both serum and cerebrospinal fluid. The pH was determined in both types of samples within two hours of collection by means of a Beckman Model 6 pH Meter, using the sealed hypodermic type of glass electrode. Blood pH was converted to the equivalent at 38°c. by means of a table formulated by Rosenthal.[15] A correction factor was also subtracted from the cerebrospinal fluid samples to convert all pH determinations to 38°c. This factor, which was determined by us as the average of five analyzed samples of normal cerebrospinal fluid, was determined according to the method used by Rosenthal[15] for other body fluids. It was: cerebrospinal fluid pH at 38°c. = pH-0.0093 (38-T) where T = temperature in °c. The correction factor for cerebrospinal fluid pH thus varied from 0.06 when room temperatures were 32°c. (blood correction factor was 0.07) to 0.14 when room temperatures were 23°c. (blood correction factor was 0.21).

Studies in Animals. Acute and subacute elevation and reduction of serum sodium and potassium were produced in dogs, specimens of cerebrospinal fluid being obtained at regular intervals during the procedure from the cisterna magna. Blood and cerebrospinal fluid urea was determined on dogs 11 and 12 by the method of Karr.[13] This "neutral" substance was analyzed in order to detect dehydration and "concentration" of the fluids studied.

A single electrolyte disturbance was produced in one animal at a time as follows:

Hyperkalemia: Dogs 1 and 2 received isotonic (1.14 per cent) potassium chloride intravenously from a buret at the rate of 10 cc. per minute until the animal died (average twelve minutes). Cerebrospinal fluid and blood specimens were obtained at one- to five-minute intervals. Dogs 3, 15 and 17 received the same solution at the rate of 4 cc. per minute until death (210, 60 and 180 minutes, respectively). Specimens were obtained at ten- to thirty-minute intervals.

Hypokalemia: Dogs 13 and 16 were placed on a semi-starvation, low potassium (200 mg. per day) diet, and 25 mg. of desoxycorticosterone acetate (cortate®)* daily was administered intramuscularly for fourteen days to each dog. At the end of fourteen days in dog 13, under pentobarbital anesthesia, 1,000 ml. of 10 per cent glucose-in-water solution was given intraperitoneally over a fifteen-minute period to lower the serum potassium further, and simultaneous cerebrospinal fluid blood samples were obtained at thirty-minute intervals until death two hours later. All specimens were analyzed for sodium, potassium and pH.

Hypernatremia: Dogs 5, 6, 7, 8, 10, 11 and 12 received an infusion of 5 per cent sodium chloride at rates varying from 1 to 10 cc. per minute until they died (360, 370, 30, 120, 180, 120 and 120 minutes, respectively). Specimens were collected at thirty- to sixty-minute intervals. Continuous electrocardiograms were obtained during all experiments.

RESULTS

Normal Human Subjects. (Table I.) The serum potassium levels in the twenty normal subjects ranged from 3.49 to 5.16 mEq./L. with a mean of 4.45 mEq./L. The cerebrospinal fluid potassium concentration in these patients ranged from 2.33 to 4.59 mEq./L. with a mean of 2.96 mEq./L. The serum cerebrospinal fluid gradient therefore averaged 1.49 mEq./L. or about 34 per cent of the serum potassium. The serum sodium levels ranged from 131 to 160 mEq./L. with a mean of 140.6 mEq./L. The cerebrospinal fluid sodium levels ranged from 128 to

* Cortate® was supplied by the Schering Corp., Bloomfield, N. J.

152 mEq./L. with a mean of 141.2 mEq./L. There is therefore no significant difference between cerebrospinal fluid sodium and serum sodium concentration. The values for cerebrospinal fluid sodium and potassium closely correspond to those previously reported[11,12]

Patients with Central Nervous System Disease. (Tables I and II.) Abnormalities, although not striking, were found in some patients. High potassium values, which might be anticipated in patients with hemorrhage into the subarachnoid space and subsequent hemolysis, were not found.

TABLE I

CEREBROSPINAL FLUID AND SERUM ELECTROLYTES IN NORMAL PATIENTS AND PATIENTS WITH CENTRAL NERVOUS SYSTEM DISEASE

		Serum			CSF		
		K (mEq./L.)	Na (mEq./L.)	pH	K (mEq./L.)	Na (mEq./L.)	pH
Normal patients (20)	Mean	4.46	140.6	7.40	2.96	141.2	7.32
	Standard deviation	0.45	7.4	0.06	0.45	6.0	0.09
	Range	3.49–5.16	131–160	7.26–7.48	2.33–4.59	128–152	7.13–7.46
Cerebral hemorrhage (10)	Mean	4.58	145.2	7.39	2.78	154.4	7.18
	Standard deviation	1.08	5.6	0.07	0.55	13.1	0.08
	Range	3.62–6.94	133–152	7.25–7.49	1.95–3.66	140–187	7.11–7.26
Acute encephalomalacia (10)	Mean	4.55	146.1	7.45	2.74	143.3	7.28
	Standard deviation	0.53	9.4	0.06	0.40	8.1	0.10
	Range	3.38–5.33	129–165	7.38–7.59	2.02–3.21	123–153	7.21–7.56
Tuberculous meningitis (5)	Mean	4.01	132.2	7.46	3.12	164.8	7.30
	Standard deviation	0.61	5.0	0.08	0.90	34.0	0.08
	Range	3.35–5.01	123–137	7.33–7.57	1.87–4.41	135–221	7.19–7.39
Hypertensive encephalopathy (5)	Mean	4.61	131.4	7.40	2.72	144.4	7.30
	Standard deviation	0.67	20.6	0.08	0.24	6.2	0.05
	Range	3.67–5.74	93–149	7.29–7.51	2.49–3.03	135–150	7.25–7.39

when the flame photometer was used. The cerebrospinal fluid pH varied from 7.13 to 7.46 with a mean of 7.32, and the serum pH from 7.26 to 7.48 with a mean of 7.40. The mean difference was therefore 0.08. Statistically, this difference was significant, as the probability that the difference was due to chance is less than 0.001. Further study is now in progress to determine the clinical and biochemical significance of this apparent difference. Venous blood, rather than arterial blood, was used in our study because of the ease of obtaining the former. Simultaneous arterial and venous pH determinations in ten patients showed no significant difference in the two types of blood when care was taken to prevent muscular exercise, prolonged venous obstruction, overheating and other factors which are known to decrease venous pH locally.

The cerebrospinal fluid potassium concentration in patients with cerebral hemorrhage averaged 2.78 mEq./L., a value which is not significantly different from normal.

No significant changes in cerebrospinal fluid and serum potassium levels were noted in patients with hypertensive encephalopathy and acute encephalomalacia. The mean serum sodium was significantly low in our cases of tuberculous meningitis (132.2 mEq./L.). High mean cerebrospinal fluid sodium was found in patients with cerebrospinal hemorrhage (154.4 mEq./L.) and tuberculous meningitis (164.8 mEq./L.). The latter value is interesting in view of the reported diminution in cerebrospinal fluid chloride in tuberculous meningitis.[14]

The mean cerebrospinal fluid pH was low in patients with cerebral hemorrhage (7.18) and

seemed to be related to the prognosis in the individual case. A falling pH usually seemed to indicate a grave prognosis. The lowest cerebrospinal fluid pH recorded during life in one of these patients was 7.02. Serum and cerebrospinal fluid in the other central nervous system diseases studied were statistically within normal limits. (Table II.)

TABLE II

STATISTICAL ANALYSIS OF ELECTROLYTES IN NORMAL AND ABNORMAL PATIENTS

Group	Serum			CSF		
	K	Na	pH	K	Na	pH
Mean of cerebral hemorrhage group (10) minus mean of normal group (20)	+0.13	+4.6	−0.01	−0.18	+13.2	−0.15
"t"	0.43	1.64	0.41	0.94	3.67	4.35
Probability of "t"	0.7	0.1	0.7	0.4	0.001	Less than 0.001
Conclusion †					**	**
Mean of acute encephalitis group (10) minus mean of normal group (20)	+0.09	+5.5	+0.05	−0.22	+2.1	−0.05
"t"	0.46	1.67	1.88	1.27	0.78	1.22
Probability of "t"	0.6	0.1	0.07	0.2	0.4	0.2
Conclusion †						
Mean of tuberculous meningitis group (5) minus mean of normal group (20)	−0.45	−8.4	+0.06	+0.16	23.6	−0.03
"t"	1.78	2.27	1.67	0.53	2.81	0.58
Probability of "t"	1.09	Less than 0.02	0.1	0.6	0.01	0.6
Conclusion †		*			**	
Mean of hypertensive encephalitis group (5) minus mean of normal group (20)	+0.15	−9.2	−0.002	−0.24	+3.2	−0.02
"t"	0.57	1.56	0.06	1.13	1.03	0.47
Probability of "t"	0.6	0.1	0.9	0.3	0.3	0.6
Conclusion †						
Mean of hyperkalemia group (8) minus mean of normal group (20)				+0.13		
"t"				0.76		
Probability of "t"				0.5		
Conclusion †						
Mean of hypernatremia group (3) minus mean of normal group (20)					+30.5	
"t"					7.09	
Probability of "t"					Less than 0.001	
Conclusion †					**	

† Under "conclusion," a blank space means the difference is not significant and could easily have been caused by chance; * means the difference is significant at the 5 per cent level but not at the 1 per cent level and therefore conclusions may be reached only tentatively; ** means the difference is highly significant and conclusions may be reached with great confidence.

Patients with Electrolyte Imbalance. (Tables II and III.) Twenty patients with varying degrees of electrolyte imbalance were studied. All of these had clinical and laboratory evidence of uremia; this state was associated with the following electrolyte disturbances occurring either alone or in combination: hypokalemia (two patients), hyperkalemia (eight patients), hypernatremia (three patients), hyponatremia (one patient), low CO_2 combining power with normal K, Na and pH (five patients), and low pH alone (one patient). The cerebrospinal fluid potassium remained within the narrow range of normal in spite of wide variations of serum potassium in both hypokalemia and hyperkalemia. In this group the highest serum potassium recorded was 7.16 mEq./L. (cerebrospinal fluid potassium was 3.55 mEq./L. in this case) and the

lowest was 1.97 mEq./L. (cerebrospinal fluid potassium was 2.43 mEq./L.).

On the other hand, cerebrospinal fluid sodium levels corresponded closely to serum levels. In patients with hypernatremia, cerebrospinal fluid sodium levels were also high (means of 185 mEq./L. and 171.7 mEq./L., respectively). One patient with an extremely low serum sodium (116 mEq./L.) also had a low cerebrospinal fluid sodium (119 mEq./L.).

Five patients exhibited a low CO_2 combining power (8.3 to 14.9 mEq./L.) and one patient had a low pH (7.25) as the only chemical abnormality. These patients maintained a normal serum and cerebrospinal fluid sodium concentration. (Table III.)

TABLE III

GENERALIZED ELECTROLYTE IMBALANCE

Disease States	No. of Patients	Serum (range of values)			Cerebrospinal Fluid (range of values)		
		Na (mEq./L.)	K (mEq./L.)	pH	Na (mEq./L.)	K (mEq./L.)	pH
Uremia with:							
Hypokalemia	2	132–149	1.97–2.69	7.36–7.45	131–155	2.43–2.74	7.29–7.31
Hyperkalemia	8	116–158	5.16–7.16	7.17–7.47	119–160	2.65–3.55	7.08–7.32
Hypernatremia	3	164–185	4.06–4.22	7.36–7.47	158–179	2.90–3.43	7.21–7.29
Hyponatremia	1	116	5.88	7.25	119	2.74	7.18
Low CO_2, but normal K, Na and pH	5	132–159	3.65–5.13	7.26–7.46	130–173	2.54–3.43	7.11–7.29
Low pH, alone	1	144	5.10	7.25	133	3.18	7.27

TABLE IV

ANIMAL EXPERIMENTS

State Induced	Dog No.	Serum*				Cerebrospinal Fluid*			
		Na (mEq./L.)	K (mEq./L.)	pH	Urea (mg./100 cc.)	Na (mEq./L.)	K (mEq./L.)	pH	Urea (mg./100 cc.)
Hyperkalemia	1	158–137	4.87– 6.65	7.12–7.12	.....	164–148	3.48–3.15	7.03–7.13	.....
	2	117–135	3.78–12.4	7.23–7.27	.....	148–135	3.07–3.31	7.37–7.20	.....
	3	150–137	3.65–11.34	7.15–6.85	.....	161–149	3.20–4.30	7.26–7.11	.....
	15	159–133	3.63–13.20	7.36–7.41	.....	157–145	3.14–3.18	7.25–7.37	.....
	17	134–139	3.52– 9.90	7.42–7.06	.....	155–158	2.44–2.85	7.39–7.19	.....
Hypernatremia	10	153–386	3.18– 4.74	7.31–6.65	.....	158–288	3.12–8.22	7.26–6.81	.....
	5	134–196	3.69– 4.53	7.30–7.15	.....	151–182	3.15–4.22	7.33–7.26	.....
	6	147–213	3.68– 4.68	7.32–6.86	.....	149–205	3.02–5.26	7.17–7.22	.....
	7	146–164	3.26– 3.19	7.31–7.22	.....	144–163	3.00–3.35	7.17–7.18	.....
	8	160–264	3.47– 4.19	7.25–6.66	.....	159–213	3.06–5.66	7.29–6.96	.....
	11	153–243	3.96– 3.86	7.29–6.97	23–16	154–233	2.87–4.66	7.36–7.17	28–22
	12	153–245	3.42– 3.69	7.29–7.02	9–3	166–254	3.03–4.12	7.20–7.07	4–6
Hypokalemia	13	158–152	4.10– 1.93	7.58–7.22	3–5	158–150	3.03–2.66	7.54–7.30	3–5
	16	152–144	3.54– 2.54	7.40–7.36	.....	137–138	3.27–2.50	7.45–7.31	.....

* First figure = initial value; second figure = final value.

Animal Experiments. Elevation of the serum potassium: (Tables IV and V, dogs 1, 2, 3, 15 and 17.) Experimental elevation of the serum potassium failed to elevate the cerebrospinal fluid

potassium level beyond the normal range. Administration of isotonic potassium chloride at relatively rapid rates increased serum potassium levels from an initial mean of 3.90 to a final mean of 10.70 mEq./L. at the time of death, a mean change of +6.81 mEq./L., yet the cerebrospinal fluid potassium did not change significantly (initial mean, 3.07 mEq./L.; final mean, 3.36 mEq./L.).

Serum sodium and pH values showed no consistent changes in these experiments. The cerebrospinal fluid sodium decreased significantly from an initial mean of 157.0 mEq./L. to a final mean of 147.0 mEq./L.

Elevation of the serum sodium: (Tables IV and V, dogs 5, 6, 7, 8, 10, 11 and 12.) In contradistinction to the failure to raise the spinal fluid potassium when the serum potassium levels were raised, alteration in the serum sodium definitely affected the cerebrospinal fluid sodium levels. The rise in serum sodium evoked a lesser, but definite rise in cerebrospinal fluid sodium. Since we were unable to produce a rise in serum sodium with isotonic sodium chloride, hypertonic (5 per cent) solutions were used which when rapidly administered evoked a mean rise in serum sodium of 95.0 mEq./L., from an initial mean of 149.4 mEq./L. to a final mean of 244.4 mEq./L. Cerebrospinal fluid sodium concentrations rose from an initial mean of 154.4 mEq./L. to a final mean of 219.7 mEq./L. when the animals died, a mean change of +65.3 mEq./L.

In those animals in which hypernatremia was induced the serum and cerebrospinal fluid potassium also rose significantly. The initial mean serum and cerebrospinal fluid potassium values were 3.52 and 3.04 mEq./L., respectively; at death the mean values were 4.12 and 5.07 mEq./L., representing mean changes of +0.60 and +2.03 mEq./L., respectively.

The blood pH consistently fell (from a mean of 7.30 in the control specimen to a mean of 6.93 at the time of death, a significant mean

TABLE V

STATISTICAL SUMMARY OF ANIMAL EXPERIMENTS

	Serum			CSF		
	K (mEq./L.)	Na (mEq./L.)	pH	K (mEq./L.)	Na (mEq./L.)	pH
Hyperkalemia:						
No. of dogs	5	5	5	5	5	4
Initial mean	3.89	143.6	7.26	3.07	157.0	7.23
Final mean	10.70	136.2	7.14	3.36	147.0	7.20
Mean change	+6.81	−7.4	−0.12	+0.29	−10.0	−0.03
Standard deviation of changes	2.73	16.5	0.18	0.47	6.7	0.14
"t"	.....	0.90	1.28	1.24	3.0	0.39
Probability of "t"	.....	0.4	0.3	0.3	0.04	0.7
Conclusion	.....	No significant change	No significant change	No significant change	Significant mean decrease	No significant change
Hypernatremia:						
No. of dogs	7	7	7	7	7	7
Initial mean	3.52	149.4	7.30	3.04	154.4	7.25
Final mean	4.13	244.4	6.93	5.07	219.7	7.10
Mean change	+0.61	+95.0	−0.37	+2.03	+65.3	−0.15
Standard deviation of changes	0.56	62.1	0.20	1.44	34.7	0.17
"t"	2.63	.....	4.43	3.47	4.60	2.34
Probability of "t"	0.04	.....	Less than 0.01	Less than 0.02	Less than 0.01	0.06
Conclusion	Significant mean increase	.....	Highly significant mean decrease	Significant mean increase	Highly significant mean increase	No significant change

change of 0.37). The cerebrospinal fluid pH did not vary significantly (control mean, 7.25; final mean 7.10).

When a considerable amount of cerebrospinal fluid had been withdrawn, toward the end of these experiments, the cerebrospinal fluid pressure was apparently low as manifested by the slow egress of fluid from the needle. The fluid was not bloody or xanthochromic. Concentration or dehydration alone could not account for the rise in cerebrospinal sodium in these experiments because simultaneous determination of blood and cerebrospinal fluid urea (a "neutral" substance) failed to demonstrate significant changes consistently.

Reduction of serum potassium: (Table IV, dogs 13 and 16.) Experimental reduction of serum potassium levels did not result in a corresponding fall in cerebrospinal fluid potassium. Although the control serum and cerebrospinal fluid potassium levels were 3.54 and 3.27 mEq./L., respectively, in dog 16 and 2.54 and 2.50 mEq./L. after DOCA administration, much more significant figures were obtained in dog 13. Here the initial serum and cerebrospinal fluid potassium levels were 4.10 and 3.03 mEq./L., respectively, whereas the final levels after DOCA and 1,000 ml. of 10 per cent glucose-in-water solution intraperitoneally were 1.93 and 2.66 mEq./L., respectively. Cerebrospinal fluid potassium remained within the normal range in spite of a markedly lowered serum potassium.

COMMENTS

The possibility that alterations in cerebrospinal fluid electrolytes might account for some of the symptoms and signs of central nervous system disease is an intriguing one. Previous experimental work[1–10] upon the effects of elevated cerebrospinal fluid potassium levels suggests that if such alterations occur in disease they might well have far reaching effects. For example, raising the potassium concentration in the cerebrospinal fluid causes a marked increase in voluntary muscle tension, rise in blood pressure and rise in respiratory rate.

Contrary to a previous report[17] our results in patients with major central nervous system disease demonstrate no elevation or depression of the cerebrospinal fluid potassium. This finding is particularly surprising since in all cases of cerebral hemorrhage xanthochromic spinal fluid was found. Such xanthochromia is certainly due to hemolysis of extravasated blood, a phenomenon which is well known to produce increased potassium levels since human erythrocytes contain about twenty times as much potassium as does serum.[18] We must therefore conclude that a central nervous system potassium transfer system is present which is capable of disposing of the excessive potassium ion so released. Since the cerebrospinal fluid potassium values remained within the normal range, we cannot ascribe the symptomatology of these diseases to abnormalities in the potassium concentration in the cerebrospinal fluid.

Hypokalemia and hyperkalemia were represented by patients with severe degrees of these abnormalities yet the cerebrospinal fluid potassium levels remained within normal limits. Again, the symptoms which accompanied these disease states could not be ascribed to variation in the cerebrospinal fluid potassium levels.

Analysis of the cerebrospinal fluid in our series of normal patients confirmed the previously reported difference between cerebrospinal fluid and serum potassium concentration.[19] While this difference was at first thought to be due to the presence of significant amounts of protein-bound potassium,[16] this theory is no longer tenable since Tarail, Hacker and Taymor[12] have conclusively demonstrated that at least 95 per cent of all potassium in serum is present in ionizable form. Some active mechanism, possibly enzymatic, therefore must maintain the cerebrospinal fluid potassium at a significantly lower level than the serum potassium. The question arises whether this mechanism is one of filtration and re-absorption similar to that of the renal glomerulus and tubule, or whether cerebrospinal fluid is actively secreted by the choroid plexus, or both. Most of the evidence points to active secretion as the mode of formation of the cerebrospinal fluid.[20] We have already indicated that the cerebrospinal fluid is able to rid itself of excessive potassium released by hemolysis in the subarachnoid space. This points to the operation of a mechanism for active reabsorption of the potassium ion at least. The intravenous infusion of large amounts of potassium in the experimental animal, which produced markedly elevated serum potassium levels, did not elevate cerebrospinal fluid potassium beyond the normal range, nor did the experimental production of hypokalemia cause a corresponding fall in cerebrospinal fluid potassium. But if reabsorption of potassium from the cerebrospinal fluid were the only active mechanism in the determina-

tion of the final cerebrospinal potassium level, there should have been some indications, eventually, of overloading when large amounts of potassium were administered.

Passive filtration alone, of course, could not account for either of these phenomena. A mechanism of active selective secretion, or transfer of this ion into the cerebrospinal fluid, is more likely. We therefore believe that both active secretion and possibly active reabsorption of potassium serve as regulatory mechanisms in establishing cerebrospinal fluid potassium levels. Further studies are now in progress in our laboratory in an effort more clearly to define reabsorption as a mechanism of cerebrospinal fluid electrolyte regulation.

As mentioned, marked variation in the cerebrospinal fluid sodium level occurred in patients with electrolyte imbalance. Generally, the cerebrospinal fluid sodium value paralleled the serum sodium concentration. This was also observed in the animal experiments in which hypertonic sodium was administered intravenously. There appears to be no protective mechanism for maintaining the cerebrospinal fluid sodium at a constant level. This does not necessarily mean, of course, that sodium filters passively into the subarachnoid space. However, we have found no evidence of any regulatory mechanism that protects the central nervous system from excessive or diminished concentrations of this ion. From a teleologic point of view this might be expected, since maintenance of a constant cerebrospinal fluid potassium level is essential to the well-being of the animal, while wide variations in the cerebrospinal fluid sodium levels appear to produce little or no effect.

SUMMARY AND CONCLUSIONS

1. Comparative studies were made of sodium, potassium and pH in the cerebrospinal fluid and serum in normal human subjects, patients with central nervous system disease and patients with serum electrolyte imbalance. Similar studies were performed in normal dogs and in dogs in which the following electrolyte abnormalities were induced: hyperkalemia, hypokalemia, hypernatremia.

2. This study supports the concept that the hemato-encephalic barrier participates actively in the maintenance of homeostatic balance of cerebrospinal fluid. The data presented suggest that cerebrospinal fluid potassium balance is maintained by selective secretion of potassium, and possibly also by active reabsorption of potassium.

3. There is no evidence that the symptoms of systemic electrolyte imbalance are due to imbalance of cerebrospinal fluid potassium concentration. Clinical and experimental evidence indicates that cerebrospinal fluid potassium levels remain unchanged in spite of changing serum potassium levels. Changes in serum sodium levels, however, are almost regularly reflected in corresponding changes in cerebrospinal fluid sodium, except when catastrophic central nervous system disease is present.

4. The cerebrospinal fluid is able to maintain relatively normal electrolyte concentrations in cases of acute encephalomalacia and hypertensive encephalopathy. In tuberculous meningitis the mean serum sodium was relatively low and the mean cerebrospinal fluid sodium was high. The low pH and high cerebrospinal fluid sodium levels found in cases of cerebral hemorrhage may be related to the clinical course of the disease. High cerebrospinal fluid potassium is found neither in patients with cerebrospinal hemorrhage nor malignant hypertension with hypertensive encephalopathy, and therefore cannot be incriminated as a related factor in the etiology or symptomatology of these conditions.

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Review

Evaluation of Therapy in Shock Following Acute Myocardial Infarction*

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ACUTE myocardial infarction is frequently followed by a fall in blood pressure.[1] This is at times associated with clinical signs of shock, varying in degree from mild to severe. The appearance of shock following acute myocardial infarction is a grave prognostic sign and, when severe, is associated with a very high mortality rate.[2]

Formerly, therapy for the shock state was primarily one of watchful waiting and was limited to non-specific, supportive measures. However, in recent years the approach has changed to one of active intervention. "Specific" agents utilized have included blood or plasma given intravenously or intra-arterially, and vasopressor drugs. The relative merits of each of these agents have been the subject for much controversy.

It is the purpose of this paper to (1) propose criteria for the uniform definition of severe coronary shock; (2) report an additional group of eighty-two patients who fulfilled our criteria for severe coronary shock, and who were treated either non-specifically or with one or more of the specific agents listed; (3) review critically all of the available reports on each of the therapeutic agents mentioned.

RELATION OF INCIDENCE OF CORONARY SHOCK TO MORTALITY STATISTICS

In order to determine the incidence, natural history and expected mortality rate in severe coronary shock, we reviewed nine reports[3–11] on 650 patients treated with non-specific measures. (Table I.) However, we found it impossible to define the natural history of this syndrome. With few exceptions, no information was available on the number of patients in whom a pressor response was obtained, or in whom shock was relieved prior to death.

Because of the wide variation in the reported incidence and mortality rates in coronary shock, the reports were divided into "low incidence" and "high incidence" groups, (Table I.) In the first group the median incidence was approximately 12 per cent and the median mortality rate was 80 per cent. In the second group, the median incidence was 45 per cent and the median mortality rate was 43 per cent. It can be noted that the reported incidence and mortality rates vary inversely with each other. This was demonstrated by Rosenbaum and Levine[3] in a report on 205 patients with recent myocardial infarction. Shock was present in 54 per cent of these patients. Of those patients in shock, 44 per cent died. However, in fifty-seven patients with mild shock, the mortality rate was 26 per cent; in thirty-nine patients with moderate shock, it was 51 per cent; and in fourteen patients with severe shock, it was 93 per cent. Similarly, Agress et al.[12] found that in ten patients with mild shock, the mortality rate was 10 per cent, while in eleven patients with severe shock, it was 91 per cent. These figures indicate that the lower the reported incidence, the greater the likelihood that shock was severe. If lesser degrees of shock are included, the incidence rises and the expected mortality rate falls.

Lack of Uniformity of Criteria for Coronary Shock. Evaluation of the reports listed in Table I is complicated by lack of uniformity in the criteria

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used for determining the severity of shock. In three reports[3,4,10] no criteria were listed. Greisman and Rosenfield[11] reported twenty-five patients who had clinical signs of shock. Yet, in seven of these the blood pressure was found elevated, and in five it was normal. In a series of sixty-one patients reported by Master et al.[9] clinical signs of circulatory collapse were present, with a rapid fall in blood pressure. The mortality rate was 42 per cent. However, in a subsequent paper it was noted that when the systolic blood pressure fell below 80 mm. Hg, the patient usually died.[1]

In the remaining four reports[5–8] shock was considered present when the systolic blood pressure fell below 90 mm. Hg, and clinical evidence of circulatory collapse appeared. Some authors[2] believe that shock may occur at a higher blood pressure in previously hypertensive patients. However, Epstein and Relman[5] excluded from their series patients with the appearance of shock, but with systolic blood pressures above 90 mm. Hg, even when the arterial pressure was at times considerably below its usual level. Similarly, they excluded patients who looked well, although their systolic blood pressures were below 90 mm. Hg. They found that such patients uniformly did well. In contrast, the mortality rate was very high in those patients with signs of vascular collapse as well as severe hypotension. The reported mortality rates in Selzer's series[6] were based upon whether shock was immediate, delayed or associated with ventricular arrhythmias. In the immediate shock group severe coronary pain frequently coexisted.

Therefore, with such widely varying criteria for coronary shock, no reliable comparison of mortality statistics can be made. Similarly, it becomes almost impossible to evaluate therapy. It is axiomatic that the same strict criteria should be applied both to a control group of patients treated non-specifically and to patients receiving specific therapy. This ideal situation is best approached when the investigator contrasts his own control series with his treated patients.

TABLE I

RELATION OF INCIDENCE OF CORONARY SHOCK TO MORTALITY STATISTICS

Year	Author	Classification of Shock	Incidence of Shock in Coronary Occlusion (%)	No. of Cases Reported	Mortality
		Low Incidence			
1941	Rosenbaum and Levine	Severe	7	14	13 (93%)
1947	Mintz and Katz	Not classified	7	36	28 (78%)
1949	Epstein and Relman	S.B.P.* below 90 mm. for 1 hr. plus	15	20	17 (85%)
1952	Selzer	Early, late and with arrhythmia (S.B.P. <90 mm.)	13	69	48 (70%)
1952	Hellerstein et al.	S.B.P. below 90 mm. for 1 hr. plus	10	10	8 (80%)
1952	Cochran et al.	S.B.P. 90 mm. or less for 1 hr. plus	20	161	131 (81%)
		High Incidence			
1937	Master et al.	Not classified	45	61	25 (42%)
1941	Rosenbaum and Levine	Mild, moderate and severe	54	110	48 (44%)
1942	Rathe	Not classified	58	160	38 (24%)
1948	Greisman and Rosenfield	Not classified	44	25	18 (72%)

* S.B.P. = systolic blood pressure.

SELECTION OF CRITERIA FOR SEVERE CORONARY SHOCK

Master et al.[1] found that, except for the cases in which the systolic blood pressure fell below

80 mm. Hg, the course of the blood pressure during and after acute myocardial infarction in 205 patients was of no definite prognostic significance. When the systolic blood pressure fell below 80 mm. Hg, shock was almost always present and the patient usually died. In establishing our criteria for severe coronary shock we have therefore excluded any patient whose systolic blood pressure was above 80 mm. Hg.

However, hypotension alone is not synonymous with shock.[1,5,13] The presence of clinical signs of peripheral circulatory collapse is also necessary. Our group has found that the degree of depression of the sensorium correlates least with the severity of shock, while the urinary output is a very sensitive index of shock, both in diagnosis and in evaluating therapy. The response of the kidney to shock aids greatly in differentiating this state from simple severe hypotension.

Severe shock is at times associated with the pain of acute myocardial infarction. In such patients, relief of pain relieves the shock and most of these patients survive.[6] The early administration of oxygen may similarly help to relieve shock in some patients.[13] Therefore, patients responding to morphine and/or oxygen were excluded from our series. Patients selected for study were those who failed to show improvement in the shock state for at least one-half hour after these measures were used. This short observation interval was chosen because severe shock may become irreversible and refractory to all methods of treatment within a short period of time.[13,14] Delay in therapy beyond the minimum observation period is therefore undesirable. Severe coronary shock represents a true medical emergency.

Shock may be produced by factors other than acute myocardial infarction. The presence of these complicating factors in a patient with acute myocardial infarction introduces differing etiologies of the shock syndrome. Correction of ventricular or supraventricular tachycardia, diabetic acidosis and coma, hemorrhage, infection and severe congestive heart failure may be sufficient to relieve the shock. Under these circumstances, accurate evaluation of any other form of therapy becomes difficult. Shock may be caused by pulmonary infarction, recent cerebrovascular accident or the intravenous administration of procaine amide or of morphine sulfate.[15] The prognosis may be influenced by these events as well as by the acute myocardial infarction. If homogeneous series are to be compared, patients in whom these complications are present should be reported separately. Such patients were therefore excluded from our series. Since we believed that therapy could not be evaluated properly in terminal patients, we also excluded any patient who died within one hour after therapy was started.

For the reasons listed we chose six criteria for determining the presence of, and evaluating therapy in, severe coronary shock: (1) Acute myocardial infarction proven by electrocardiogram or autopsy or both. (2) Systolic blood pressure 80 mm. Hg or less; and pulse rate 110 or more (unless 2° or 3° A-V block present). (3) Clinical signs of peripheral circulatory collapse: marked oliguria or anuria, pallor or cyanosis or both, marked sweating, cold skin, dulled sensorium. (4) No improvement in shock state for one-half hour after relief of pain and administration of oxygen. (5) Absence of ventricular or supraventricular tachycardia, severe congestive heart failure, significant pulmonary infarction, recent cerebrovascular accident, diabetic acidosis, hemorrhage, infection and hypotensive drugs. (6) For evaluation of therapy, patient should survive at least one hour after the initiation of treatment.

PRESENT SERIES

Material. Using the criteria cited, we assembled eighty-two patients who had severe coronary shock. (Table II.) Twenty-two of these patients were treated with morphine sulfate, oxygen and general nursing care. Thirty-five patients were given "specific" therapy consisting of blood or plasma intravenously or intra-arterially, and either phenylephrine (neosynephrine®), methoxamine (vasoxyl®) or ephedrine. These fifty-seven patients were obtained by reviewing the records of the Wadsworth Veterans Hospital for the period July, 1950 to July, 1952; they constituted 9 per cent of all patients with acute myocardial infarction. The remaining twenty-five patients were treated by our group with levarterenol (levophed®) as the principal form of therapy.

Method. The group of twenty-two patients treated non-specifically were given morphine sulfate in doses of 10 to 15 mg. intravenously or subcutaneously, as indicated. Oxygen was administered continuously through a nasal catheter or a B.L.B. mask.

In the group of thirty-five patients treated

specifically, blood or plasma or both were given intravenously in total amounts of 250 to 1,250 cc., at an average rate of 4 to 5 cc. per minute. They were given intra-arterially in total amounts of 250 to 750 cc., at an average rate of 25 cc. per minute. Phenylephrine was given intravenously or intramuscularly in total doses of 5 to 25 mg., methoxamine in total doses of 30 to 50 mg., and ephedrine in total doses of 25 to 75 mg. The therapeutic distribution of the patients was as follows: ten received only blood and/or plasma intravenously; three received only blood and/or plasma intra-arterially; eleven patients received blood and/or plasma intravenously and in addition one of the previously mentioned vasopressor drugs (phenylephrine was used in nine patients, methoxamine in one patient and ephedrine in one patient). Eight patients were given only phenylephrine, two patients methoxamine and one patient ephedrine.

The last group of twenty-five patients received levarterenol as follows: The solution was prepared by diluting the contents of one ampule containing 4 mg. of levarterenol in 1,000 cc. of 5 per cent glucose, and was administered by a constant intravenous infusion. The rate of flow of this solution was adjusted to maintain the systolic blood pressure above 100 mm. Hg. The concentration of this solution was increased when necessary to limit the amount of fluid given intravenously or when the dose of levarterenol required per minute was high. In a few patients, a concentration of 24 mg. of levarterenol in 1,000 cc. of solution was eventually necessary. When protracted therapy was required, the levarterenol solution was administered through a polyethylene catheter which had been inserted at the ankle, and passed intravenously to the mid-portion of the leg.

In each of the three series of patients therapy was started within one hour of the onset of shock, with few exceptions. We defined a satisfactory pressor effect as a rise in the systolic blood pressure to above 100 mm. Hg. We considered shock relieved when the patient maintained a stable circulatory system for at least twelve hours after therapy was discontinued.

TABLE II

RESULTS OF THERAPY IN EIGHTY-TWO PATIENTS WITH SEVERE CORONARY SHOCK

No. of Cases Reported	Classification of Shock	Therapy	Pressor Effect	Relief of Shock	Survival	Mortality
22	Severe	Non-specific	5 (23%)	5 (23%)	4 (18%)	18 (82%)
35	Severe	Intravenous and intra-arterial transfusion and vasopressor drugs*	5 (14%)	4 (11)%	2 (6%)	33 (94%)
25	Severe	Levarterenol	23 (92%)	12 (48%)	8 (32%)	17 (68%)

* Phenylephrine, methoxamine and ephedrine.

Results. Table II summarizes the results of therapy in each of the three series of patients. In the series of twenty-two patients treated expectantly, a pressor effect was obtained and shock relieved, in five (23 per cent). Four of these patients ultimately survived. The mortality rate in this control series was 82 per cent.

In the second series of thirty-five patients a pressor effect was obtained in five (14 per cent). Shock was relieved in four patients (11 per cent). Of the two survivors one received blood intra-arterially, and the other received phenylephrine. The mortality rate in this series was 94 per cent. Death occurred in each of the twenty-one patients who received blood and/or plasma intravenously, with or without phenylephrine, methoxamine or ephedrine.

In the series of twenty-five patients treated with levarterenol, a pressor effect was obtained in twenty-three (92 per cent). Shock was relieved in twelve patients (48 per cent), of whom eight survived. The mortality rate in the series of patients treated with levarterenol was 68 per cent.

Comparison of Patients with and without Heart Block. Of the patients who had second or third degree A-V block, fifteen were treated with miscellaneous measures and nine with levarterenol. (Table III.) In the group of fifteen patients treated with miscellaneous measures a pressor effect was obtained and shock relieved in four (twenty-seven per cent) of whom three ultimately survived (mortality rate 80 per cent). Each of nine patients with heart block, treated with levarterenol, obtained a pressor effect.

Shock was relieved in six (67 per cent), and survival occurred in three (mortality rate 67 per cent). In both groups heart block was replaced by normal conduction in every patient in whom shock was relieved. Both heart block and shock persisted in the remaining patients.

TABLE III
COMPARISON OF RESULTS IN PATIENTS WITH AND WITHOUT HEART BLOCK

Therapy	No. of Cases Reported	Pressor Effect	Relief of Shock	Survival	Mortality
Heart Block					
Miscellaneous*	15	4 (27%)	4 (27%)	3 (20%)	12 (80%)
Levarterenol	9	9 (100%)	6 (67%)	3 (33%)	6 (67%)
No Block					
Miscellaneous*	42	6 (14%)	5 (12%)	3 (7%)	39 (93%)
Levarterenol	16	14 (88%)	6 (38%)	5 (31%)	11 (69%)

* Non-specific, intravenous and intra-arterial transfusion, phenylephrine, methoxamine, ephedrine.

Of the fifty-eight patients without heart block, forty-two were treated with miscellaneous measures and sixteen were treated with levarterenol. (Table III.) In the group of forty-two patients treated with miscellaneous measures, a pressor effect was obtained in six (14 per cent), shock was relieved in five (12 per cent) and three patients survived (mortality rate 93 per cent). Of sixteen patients without heart block who were treated with levarterenol, a satisfactory pressor effect was obtained in fourteen (88 per cent), shock was relieved in six (38 per cent) and five patients survived (mortality rate 69 per cent).

Levarterenol Series. Data on each of the twenty-five patients who were treated with levarterenol are shown in Table IV. All but one of these patients were males. Their ages varied from thirty-nine to eighty-one years; the median age was sixty-one years.

The duration of shock prior to levarterenol therapy was from one-half to one hour in twenty patients. In three patients this period was one and one-half, two and one-half and three hours, respectively. The duration of shock was unknown in two patients who were in shock on admission.

In fourteen patients, the duration of levarterenol therapy ranged from two to twelve hours, and the total dose from 1 to 41 mg. In nine patients, these values were twelve to seventy-two hours and 20 to 104 mg., respectively. Duration of therapy was 100 hours and 480 hours in the remaining two patients. The corresponding total doses of levarterenol were 105 mg. and 600 mg., respectively.

Factors Affecting Prognosis. The prognosis was found to be poor when a history of previous myocardial infarction and/or previous congestive heart failure was obtained. Eight patients had such a history; shock was relieved in only one, and none survived. In contrast, shock was relieved in eleven of seventeen patients who had neither previous myocardial infarction nor previous congestive heart failure, and eight of these patients survived.

Neither the duration of levarterenol therapy nor the total dose required were found to be valid prognostic factors. However, the amount of levarterenol required per unit of time was significant prognostically. Thus shock was relieved in ten of thirteen patients who required less than 1 mg. of levarterenol per hour; six of these patients survived. In contrast, shock was relieved and survival occurred in only two of twelve patients who required more than 1 mg. of levarterenol per hour.

The prognosis of the patients whose systolic blood pressure was imperceptible was no worse than those in whom it was 40 to 80 mm. Hg. Thus it was imperceptible in twelve patients and of these, seven were relieved of shock and five survived. The systolic blood pressure ranged from 40 to 80 mm. Hg in the remaining thirteen patients and of these, five were relieved of shock and three survived.

We found that the prognosis was not influenced by whether shock occurred early or late in the course of myocardial infarction. In thirteen patients shock occurred in the first twelve hours after myocardial infarction; shock was relieved in seven of these and four patients survived. Shock occurred later than twelve hours after myocardial infarction in twelve patients; five of these were relieved of shock and four patients survived.

Adjunctive Measures. Isopropylarterenol (isuprel®*), in doses of 0.02 to 0.04 mg. intravenously and 0.2 mg. subcutaneously, was used as an adjunct to levarterenol in four patients who had heart block. An added and significant pressor effect, associated with an increase in the previously slow ventricular rate, occurred in three of the patients; shock was relieved in two. The fourth patient had heart block and an idio-

* Supplied by Winthrop-Stearns Inc., New York, N. Y.

ventricular rate of 70. Isopropylarterenol increased his ventricular rate to 90 but failed to increase the pressor effect produced by levarterenol.

Cortisone aldehyde* in intermittent doses of 20 to 50 mg. was given intravenously to four other patients during levarterenol therapy. No additional rise in blood pressure occurred in three of the patients; a slight and transient rise occurred in the fourth.

Blood was given intra-arterially to three patients who were receiving levarterenol. Each of these patients received 500 cc. of blood at a rate of 25 cc. per minute. A slight increase in mean arterial blood pressure occurred, limited to the duration of the transfusion.

Digitalis was given intravenously to seven patients who were not in congestive heart failure, in an effort to potentiate the effect of levarterenol. No additional pressor effect occurred.

Electrocardiographic and Autopsy Findings. Recent infarction of the posterior wall occurred in fifteen patients, and of the anterior wall in ten patients. In the latter group, one patient (A. S.) who survived had electrocardiographic evidence of a recent anteroseptal subendocardial myocardial infarction. Four patients died of cardiac tamponade secondary to myocardial rupture and hemopericardium. In two, this occurred after shock had been relieved. Massive myocardial infarction, predominantly posterior wall, was found at autopsy in three patients (H. S., G. F. S. and A. H.). Bilateral adrenal hemor-

TABLE IV

TWENTY-FIVE PATIENTS WITH SEVERE CORONARY SHOCK TREATED WITH LEVARTERENOL

Patient	Age	Blood Pressure before Therapy	Therapy				Results			Death (hr.) after Onset Shock
			Started		Duration (hr.)	Total Dose (mg.)	Pressor Effect	Shock Relieved	Survival	
			After Infarct (hr.)	After Shock (hr.)						
S. J. D.	70	0*	24	1½	2	1	+	+	+	.....
T. H.	40	0	1	1	7	2	+	+	+	.....
A. S.	64	0	½	½	7	4	+	+	+	.....
G. B.	54	70/50	12	†	8	5	+	+	+	.....
S. C. H.	71	0	14	½	4	6	+	+	+	.....
E. F. S.	64	0	24	½	27	24	+	+	+	.....
A. G. M.	60	80/50	48	1	60	30	+	+	+	.....
G. J. B.	45	78/54	7	1	100	105	+	+	+	.....
C. G.	66	0	5	½	2	1	+	+	0	13
D. S.	53	0	48	†	7	3	+	+	0	456
H. S.	67	70/50	11	½	26	20	+	+	0	72
W. H. W.	67	50/?	2½	2½	71	34	+	+	0	240
L. E. E.	60	40/?	5½	1	2½	6	+	0	0	3½
M. S.	45	0	24	1	7	6	+	0	0	8
C. A.	65	0	24	1	3	7	+	0	0	4
J. H.	61	64/50	6	3	12	22	+	0	0	18
I. A.	56	60/?	48	1	72	23	+	0	0	73
S. V.	52	0	2½	½	16	29	+	0	0	22
W. F. H.	81	80/40	23	1	16	36	+	0	0	17
T. F. S.	56	70/?	12	½	8	41	+	0	0	8½
G. F. S.	62	70/?	24	½	48	44	+	0	0	49
D. A. H.	48	60/?	34	½	33	104	+	0	0	34
A. H.	39	80/50	22	1	480	600	+	0	0	481
L. D. Z.	62	0	9	1	1½	2	0	0	0	2½
W. M. M.	74	0	1	½	6	22	0	0	0	6½

* 0 = blood pressure imperceptible.

† In shock on admission; duration of shock unknown.

* Supplied by Merck & Co. Inc., Rahway, N. J.

rhage accounted for the death of patient W. H. W. approximately nine days after shock had been relieved. Only the original anterior wall infarction was found in patient D. S., who died suddenly nineteen days after shock had been relieved.

TABLE V

REPORTS ON THERAPY OF CORONARY SHOCK

Year	Author	No. of Cases Reported	Pressor Effect	Relief of Shock	Survival	Mortality
			Intravenous Transfusion			
1949	Epstein, Relman	30	11 (37%)	.....	3 (10%)	27 (90%)
1949	Sampson, Singer	11	8 (72%)	4 (36%)	1 (9%)	10 (91%)
1952	Cochran	18	.....	4 (22%)	2 (11%)	16 (89%)
			Intra-arterial Transfusion			
1951	Silber et al.	9	8 (88%)	5 (55%)	2 (22%)	7 (78%)
1952	Berman, Akman	8	4 (50%)	3 (38%)	1 (13%)	7 (87%)
1952	Cochran et al.	25	19 (76%)	12 (48%)	5 (20%)	20 (80%)
			Phenylephrine and Intravenous Transfusion			
1953	Gootnick, Knox	32	21 (66%)	.....	14 (44%)	18 (56%)
			Mephentermine			
1952	Hellerstein et al.	17	15 (88%)	13 (76%)	6 (35%)	11 (65%)

LITERATURE REVIEW

To compare our results with those found in the literature we reviewed seventeen reports from 1949 to 1954 on 255 patients in whom shock was associated with acute myocardial infarction. These patients were treated with transfusion and/or vasopressor drugs. Again, lack of uniformity was found in the criteria used to determine the severity of shock. In addition, the term "relief of shock" was frequently not defined. Comparison of one series with another must therefore be made with reservation.

Intravenous Transfusion. Three series[5,16,17] totalling fifty-nine patients in whom the sole specific therapy was blood or plasma administered intravenously have been reported. (Table v.) The average amounts given were 350 to 700 cc., and the average rate of flow was 4 cc. per minute. Despite a variable pressor effect, the percentage of patients in whom shock was relieved was not increased. The mortality rate was no better than with non-specific therapy. In one series,[17] the results with intravenous transfusion were distinctly poorer than in the control series treated non-specifically.

Intra-arterial Transfusion. Three series[8,18,19] totalling forty-two patients treated by intra-arterial transfusion alone have been reported. (Table v.) The average amounts given were 400 to 600 cc., and the average rate of flow was 25 cc. per minute. Advantages claimed for this method are increased safety, more rapid delivery of blood, more direct coronary filling, stimulation of respiratory centers, and rapid return of kidney function.[18] A pressor effect was obtained in thirty-one of the forty-two patients (74 per cent). Shock was relieved in twenty patients (48 per cent). Survival occurred in eight patients. The mortality rate of 81 per cent for the three series was no better than would be expected with non-specific therapy alone. The importance of comparing similar groups of patients is shown

by the results in a control series of fifty patients treated non-specifically by Cochran.[17] Shock was relieved in 42 per cent and the mortality rate was 76 per cent. The results were similar in the series of twenty-five patients given intra-arterial transfusion by Cochran et al.[8] Shock was relieved in 48 per cent and the mortality rate was 80 per cent.

Phenylephrine and Intravenous Transfusion. Gootnick and Knox[20] treated thirty-two patients with phenylephrine and intravenous transfusion. (Table v.) Phenylephrine was given intravenously or intramuscularly in intermittent doses of 2 to 7 mg. Blood or plasma were given intravenously in total amounts of 250 to 1,500 cc. A pressor effect was obtained in twenty-one of the thirty-two patients (66 per cent). While the number of patients in whom shock was relieved was not stated, fourteen patients survived. The mortality rate was 56 per cent. Data of a comparable control series were not presented. In the treated series neither phenylephrine nor intravenous transfusion alone was as effective as the two used together. The average total dose of phenylephrine used in the survivors (80 mg.) was almost twice that used in the non-survivors (44 mg.). These authors stressed the importance of early therapy. In their series the average duration of shock prior to therapy was three hours in those patients who survived and thirteen and one-half hours in those who died.

Mephentermine. Hellerstein et al.[7] treated seventeen patients with mephentermine (wyamine®). (Table v.) This was administered either in a continuous intravenous infusion at a rate of 1 mg. per minute, or in intermittent doses of 5 to 20 mg. intravenously and 35 mg. intramuscularly. A pressor effect was obtained in fifteen patients (88 per cent), shock was relieved in thirteen patients (76 per cent) and six patients survived (mortality rate 65 per cent). The importance of comparing patients with similar degrees of shock was demonstrated when the severity of the shock was graded. With shock of 4 plus severity, six of seven patients died (mortality rate 86 per cent). With shock of 3 plus severity, five of nine patients died (mortality rate 55 per cent). The remaining patient, who had shock of 2 plus severity, survived.

TABLE VI

REPORTS ON LEVARTERENOL THERAPY OF CORONARY SHOCK

Year	Author	No. of Cases Reported	Pressor Effect	Relief of Shock	Survival	Mortality
1953	Gazes et al.	7	7 (100%)	7 (100%)	6 (86%)	1 (14%)
1953	Smith and Guz	6	6 (100%)	4 (67%)	4 (67%)	2 (33%)
1953	Miller et al.	9	8 (88%)	5 (56%)	5 (56%)	4 (44%)
1954	Sampson and Zipser	30	27 (90%)	20 (67%)	16 (53%)	14 (47%)
1953	Moyer et al.	14	12 (85%)	6 (42%)	6 (42%)	8 (58%)
1952	Kurland and Malach	14	10 (71%)	9 (64%)	4 (29%)	10 (71%)
1953	Livesay and Chapman	6	5 (83%)	1 (17%)	1 (17%)	5 (83%)
1953	Calenda et al.	13	9 (70%)	4 (31%)	2 (15%)	11 (85%)
1952	Miller and Baker	7	4 (57%)	1 (14%)	1 (14%)	6 (86%)
Total	.....	106	88 (83%)	57 (54%)	45 (42%)	61 (58%)

Levarterenol. Table VI summarizes the results of levarterenol therapy in 106 patients comprising nine reports.[21–29] The percentage of patients in whom a pressor effect was obtained varied from 57 to 100 per cent. Much greater variations occurred in the percentage of patients in whom shock was relieved (14 to 100 per cent), and in the mortality rates (14 to 86 per cent). This wide variation in reported results may be due to the following factors: (1) Difficulty in assessing the severity of shock and in defining relief of shock in the absence of uniformly accepted criteria: the inclusion of patients with lesser degrees of shock will lower the mortality rate. If this occurs, it becomes difficult to evaluate the effects of therapy. (2) Variation in the duration of shock before therapy is started: excessive delay in initiating therapy may raise the mortality rate.[2,13,20,23] On the other hand, patients with severe hypotension alone have been treated with levarterenol to prevent clinical shock. There is no way of determining in which of these patients signs of shock would develop if specific therapy

were withheld. Patients with severe hypotension alone have a lower mortality rate than those with both clinical shock and severe hypotension.[5] (3) Numerically small series: two of the series consisted of six patients, and two consisted of seven patients. In a small series, the results in one or two patients have a disproportionate influence percentagewise. In our series, shock was relieved in four (66 per cent) of the first six patients whom we treated with levarterenol, and survival occurred in three (50 per cent). In our next ten patients shock was relieved in three (30 per cent) and survival occurred in one (10 per cent). In our next nine patients, shock was relieved in five (56 per cent) and survival occurred in four (44 per cent). These variations in results occurred in spite of the fact that all of our patients met the same criteria for severe coronary shock.

Within these limitations, we have combined the experience of nine groups of investigators who treated 106 patients with levarterenol. A pressor effect was obtained in eighty-eight (83 per cent), shock was relieved in fifty-seven (54 per cent) and forty-five patients survived (mortality rate 58 per cent). By adding our series of twenty-five patients, the total was increased to 131 patients treated with levarterenol. A pressor effect was obtained in 111 of the 131 (85 per cent), shock was relieved in sixty-nine (53 per cent) and survival occurred in fifty-three (mortality rate 60 per cent).

COMMENTS

The prognosis of a patient in whom shock develops following acute myocardial infarction may be influenced by many factors. In such a patient shock may be produced by pain, ventricular or supraventricular tachycardia, congestive heart failure, hemorrhage, infection, hypotensive drugs and by such diseases as pulmonary infarction, cerebrovascular accident and diabetic acidosis. In addition, the clinical course depends on the severity and duration of shock. To establish criteria for the classification of shock one must take into account all of the variables mentioned as well as the fact that severe hypotension alone is not synonymous with shock. Otherwise, comparison will be made between heterogeneous groups of patients. Much of the variation in results reported in the literature is due to lack of uniformity in the definition and classification of coronary shock as well as reporting of statistically small series.

The efficacy of therapy in coronary shock is judged not only by its effect on the mortality rate but also upon whether shock is relieved and a pressor effect produced. Few control data are available concerning the latter two events. A pressor response to therapy is encouraging, particularly when it is associated with significant clinical improvement. However, it does not necessarily signify that shock has been relieved. The term "relief of shock" should be clearly defined and should be reserved for those patients who maintain a stable circulatory system with no clinical evidence of shock for a significant period of time after therapy has been discontinued.

Proper evaluation of a therapeutic procedure can be made only if the same clearly defined criteria are applied to the control series and to the treated series of patients. Unless the investigator reports his own control series, this requirement may not be met. This ideal approach is limited in that no one group of investigators has treated a very large series of patients who have severe coronary shock. A clearer picture of the value of any agent would be obtained if all investigators, using the same criteria, reported comparable control series.

Neither our results nor those reported in the literature reveal any evidence that intravenous transfusion alone is of value in the treatment of severe coronary shock. In some instances patients so treated fared worse than did comparable patients who were treated non-specifically. Intra-arterial transfusion may be associated with a significant although frequently transient, pressor effect. However, intra-arterial transfusion was not associated with a higher incidence of relief of shock or of survival when compared to a valid control series.

To date, the most encouraging results have been reported with vasopressor therapy. Beneficial effects have been attributed to phenylephrine combined with intravenous transfusion[20] and to methentermine.[7] Oblath and Griffith,[30] however, found that phenylephrine, methentermine and methoxamine were not suited for use in a constant intravenous infusion, and were too rapidly metabolized for intermittent use. They reported that both methentermine and methoxamine lost their effectiveness relatively early in shock. Data are now available on 131 patients with coronary shock who were treated with levarterenol administered by a constant intravenous infusion. The prompt pressor response

obtained in five of every six patients so treated makes levarterenol the vasopressor drug of choice. Relief of shock occurred in one-half of patients treated with levarterenol and in only one-fourth of patients treated expectantly. Survival occurred in two-fifths of patients treated with levarterenol and in only one-fifth of patients treated expectantly.

Further data are necessary to determine whether levarterenol is of greater benefit in patients with heart block than in those with normal A-V conduction. Heart block associated with ventricular bradycardia increases the severity of shock, and is in turn perpetuated by the latter.[6] Levarterenol, by its pressor effect, may break this vicious cycle by increasing oxygen tension of ischemic muscle.[31] A-V conduction may thus be sufficiently improved to eliminate the block present. The significance of this is demonstrated by the fact that in our series of patients with A-V block relief of shock was obtained only when the block was eliminated.

Of the adjunctive measures used by us only parenterally administered isopropylarterenol was of value. The latter drug, used in the presence of heart block, significantly potentiated the pressor response of levarterenol, apparently by increasing a previously slow ventricular rate. Neither cortisone aldehyde given intravenously nor blood given intra-arterially improved the pressor effect of levarterenol. Digitalis, in the absence of congestive heart failure, did not increase the pressor effect of levarterenol. In contrast, prompt digitalization is indicated and may be life-saving when shock and congestive heart failure occur together.[2,32]

The mechanism of coronary shock remains obscure.[2,13] Because of this, present day therapy is largely empirical. The relative importance, in the pathogenesis of coronary shock, of decreased cardiac output, cardiopulmonary reflexes and peripheral vascular collapse remain to be assessed. Few data are available on the hemodynamic changes that occur in these patients. In two series[33,34] totalling ten patients cardiac output was found to be uniformly low in the presence of coronary shock. However, similarly low values were at times found following acute myocardial infarction in the absence of shock. The total peripheral resistance was increased in six of the ten patients with coronary shock. In the remaining four patients it was no greater in the presence of shock than in its absence. Blood volume studies in patients with coronary shock[12,33,34] have shown that the blood volume may be decreased, normal or increased. The results depend upon the severity of the shock as well as upon its duration. The available data indicate that failure of peripheral response as well as decreased cardiac output are two of the factors responsible, in varying degrees, for the development of coronary shock. The response to therapy may be dependent upon which of these hemodynamic changes predominates. Vasopressor drugs may help those patients who have a normal or relatively low total peripheral resistance. They would be less likely to benefit those patients in whom total peripheral resistance is very high, and indeed may be harmful to such patients.[33,35] Similarly, poorer results are to be expected from intravascular transfusions in patients with normal or high blood volumes than in patients with low blood volumes. Additional data on the basic changes associated with coronary shock are needed to provide a more comprehensive approach to this problem and to help decrease further the high mortality rate associated with it.

SUMMARY

1. There is need for uniform criteria for the classification of shock following acute myocardial infarction.

2. Levarterenol is the vasopressor drug of choice in patients with severe coronary shock. Compared to non-specific therapy, levarterenol is beneficial and may be life-saving in an additional 20 per cent of these patients.

3. Neither intravenous nor intra-arterial transfusion alone reduces the mortality rate in severe coronary shock.

4. The mechanism of coronary shock is obscure and present day therapy is empirical. Additional data are needed on the hemodynamic changes and mechanism of this syndrome.

Addendum: Since this paper was prepared for publication, two additional clinical studies have been reported. Griffith et al.[36] published their experiences in the treatment of coronary shock and stressed the importance of early therapy. Gilbert et al.[37] reported studies of the hemodynamic changes in seven patients with coronary shock; two of these patients were in severe shock.

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Seminars on the Hemolytic Anemias

Hereditary Hemolytic Disorders Associated with Abnormal Hemoglobins*

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THE normal human erythrocyte has the shape of a biconcave disc. Characteristic shape anomalies such as spherocytosis, leptocytosis (target cells), drepanocytosis (sickle cells), elliptocytosis or acanthrocytosis[1] have long been noted in hereditary diseases. But not until recently has it been feasible to correlate some of these shape anomalies with the presence and properties of specific abnormal erythrocyte constituents. The fundamental discovery by Pauling et al.[2,3] in 1949 established that the sickling phenomenon of red cells is dependent upon a pathologic variety of the hemoglobin (Hb) molecule. Other types of human Hb have also been found;[4–8] to-date, six *abnormal* variants of the red cell pigment are known to exist in addition to the two types, normal adult and fetal, which are encountered under physiologic conditions. Fetal Hb, a compound recognized for almost a century but until recently not considered to be of any pathologic importance, is also involved in some hematologic disorders of adult life.[9,10]

At the beginning of the research on abnormal Hb's complicated and expensive technics for their identification had to be employed which were not available to the average hospital laboratory. But soon relatively simple procedures evolved which now permit and, indeed, compel the use of Hb analysis in the routine work-up of suspected hereditary hematologic disturbances. As a further sequel to this technical progress geneticists and anthropologists have become increasingly concerned with these abnormal proteins, since the genetic determinants responsible for their propagation show significant ethnic variations.

Terminology (Table 1). Rapid development in a new scientific field is frequently beset with difficulties in nomenclature. In January, 1953, at a symposium on Hb abnormalities sponsored by the Hematology Study Section of the United States Public Health Service, the symbols A for normal adult, F for fetal, S for sickle cell Hb, and C and D for the two other abnormal pigments known at that time were recommended for general use.[11] It was also considered that if new types of human Hb should be discovered they should be assigned letters of the alphabet in the order of their discovery, beginning with the letter E, unless, as is the case with sickle cell or with fetal Hb, there is some characteristic feature associated with the pigment which will serve as the basis for a convenient mental association. In 1954 two new pathologic Hb's, types E[6,7] and G,[8] were recognized. The designation Hb M is proposed by the author for a spectroscopically abnormal *met*-Hb, first described by Hörlein and Weber[12] in 1948 in a family with hereditary methemoglobinemia.

TABLE 1
TERMINOLOGY OF HEMOGLOBINS[11]

Type of Hb	Symbol
Normal adult	A
Fetal	F
1st Pathologic (sickle cell) Hb	S
2nd Pathologic Hb	C
3rd Pathologic Hb	D
4th Pathologic Hb	E
5th Pathologic Hb	G
Pathologic Met-Hb	M

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DISTINCTIVE FEATURES OF THE HUMAN HEMOGLOBIN TYPES

Hb is composed of four heme molecules which are attached to the protein moiety, globin. The hemes impart the red color to the protein. Their configuration (iron-protoporphyrin) and mode of attachment are identical throughout the vertebrate animal kingdom but the globin fraction exhibits species specificity.[13,14] The dissimilarities of the human Hb types also reside in the protein part.[2,14,15] They have been uncovered by the application of methods generally used for the characterization of proteins, such as electrophoresis, resistance to denaturing agents, solubility studies, spectroscopic and immunologic behavior, amino acid composition, etc. Only the most important data can be mentioned here.

1. Electrophoresis. As can be seen from Figure 1, with the moving boundary technic at pH 6.5[16] Hb A moves slowest, Hb C fastest and Hb S has an intermediate mobility. Fetal Hb cannot be distinguished from normal adult pigment, nor can Hb S from Hb D. Hb E has a mobility slightly slower than that of Hb S.[6] The specific mobility constants and isoelectric points of the pigment variants,[3,16–18] as far as they are known, may be found in Table II. Although *special* procedures permit separation of Hb F

TABLE II
DIFFERENCES OF HUMAN HEMOGLOBIN TYPES

Technic	Types						
	A	F	S	C	D	E	G
Electrophoretic mobility ($\times 10^{-5}$ cm.^{2}/volt/sec.), pH 6.5	2.4	2.4	2.9	3.2	2.9	between A and S	—
Isoelectric point: CO Hb	6.87	6.94–7.0	7.09	7.30	7.09	—	—
Paper electrophoresis, pH 8.6		faster than S	faster than C	slowest	like S	between S and C	between A and S
Relative mobilities	fastest	slower than A	slower than A				
Resistance to alkali denaturation	not resistant	resistant	not resistant				
Solubility of reduced Hb, Gm./liter, pH 6.8 phosphate buffer	S < D < A = E < F < C						—
Tactoid formation	absent		present	absent	—	—	—
Polymerization with S Hb	present	absent	present		—	—	—
Spectroscopy	tryptophan band		like A			—	—
	2910 Å	2898 Å					
Immunology: specific sera	available		not available	—	—	—	—
Terminal end groups	(5) valyl	(2) valyl	(5) valyl		—	—	—
Free SH groups	2	—	3	—	—	—	—
Free COOH groups	—	—	2–4 less than A	5–8 less than A	—	—	—

— Indicates data not yet available.

from Hb A in the Tiselius apparatus,[19] this approach is not practical since the embryonic pigment can be determined much simpler by the alkali denaturation technic.[9] The electrophoretic patterns most commonly encountered in the U.S.A. are also depicted in Figure 1.

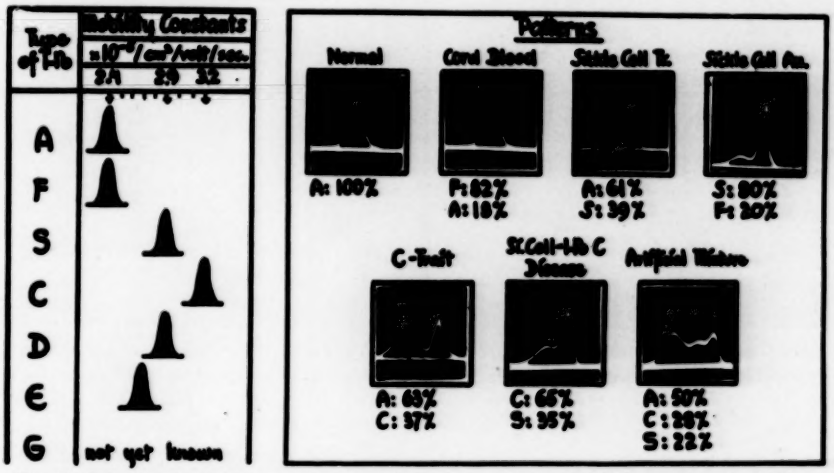

FIG. 1. Moving boundary electrophoresis patterns of the different hemoglobins. Ascending boundaries; the migration proceeds from left to right; cacodylate buffer pH 6.5, 0.1 ionic strength. Hb D, E and G were not available for study.

Attention is drawn to the presence of a non-S Hb fraction in sickle cell anemia.[20] This particular fraction is composed in its entirety of alkali-resistant type F Hb. An identical electrophoretic pattern is obtained in sickle cell-thalassemia disease but the non-S fraction is then composed predominantly of Hb A and, to a lesser extent, of the fetal pigment.[21–23] These findings indicate that Hb analysis by means of electrophoresis may be inadequate, and that additional technics must also be employed for closer differentiation of the various compounds.

Electrophoresis of hemolysates on filter paper has established Hb analysis as a routine laboratory procedure. Several types of inexpensive apparatus have been described. The "hanging-strip" set-up of Durrum was used by Spaet[24] who first applied paper electrophoresis to Hb solutions. Smith and Conley[25] employed a modification of the apparatus of Kunkel and Tiselius.[26] Their technic has also given excellent results in the author's laboratory.

One drop of the hemolysate (we use a 10 gm. per cent Hb solution) is placed in the middle of a strip of Whatman No. 3 MM filterpaper, previously moistened with veronal buffer pH 8.6, ionic strength 0.06. The paper is sandwiched between glass plates which then are sealed with lubriseal and kept under firm and constant pressure by means of clamps. The free ends of the paper strip are immersed into the buffer solution placed in appropriate plastic containers. Platinum wire electrodes and a current from a power supply (350 volts) are used. Sufficient separation of the various components to diagnose the pattern is achieved within about two hours. Staining of the proteins with bromphenol blue is recommended if the strips are to be filed for future reference.

The relative mobilities of the various Hb types and the most commonly encountered combinations are visualized in Figures 2 and 3. Since the pH of the buffer is on the alkaline side of the isoelectric points of these proteins, Hb A moves fastest, Hb C slowest, and Hb S exhibits an intermediate mobility. If larger amounts of Hb F are present together with Hb A, they can be readily recognized since the fetal pigment has a slightly slower mobility than normal adult Hb. Complete separation of these particular components is, however, never achieved. Type S and type D Hb have identical mobilities.[18] Hb E has an intermediate mobility between those of C and S[6,7] (Fig. 3); Hb G[8] has been reported to be located between the A and S compounds after sufficient separation.

The simple technic of paper electrophoresis of hemolysates is ideally suited for mass surveys since a practically unlimited number of specimens can be examined simultaneously. The equipment needed is inexpensive and no specially trained personnel is required. Quantitative determinations of the Hb compounds, even with longer runs (fifteen hours, 250 volts) to

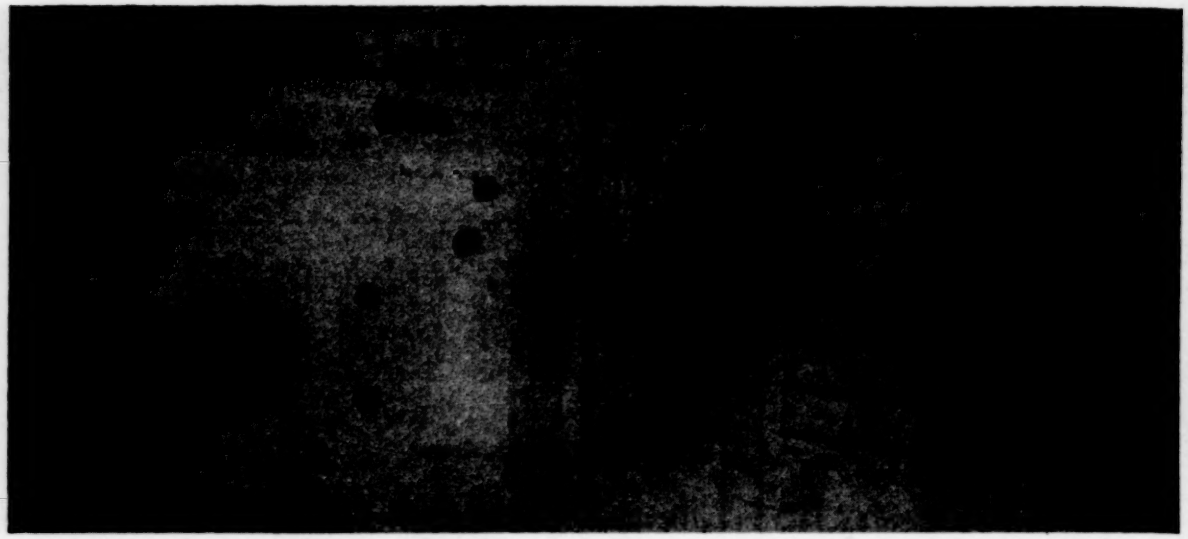

FIG. 2. Relative mobilities and common hemoglobin patterns as obtained with paper electrophoresis. The migration proceeds from left to right. The Hb patterns represent the findings in the disorders most commonly occurring in the United States.

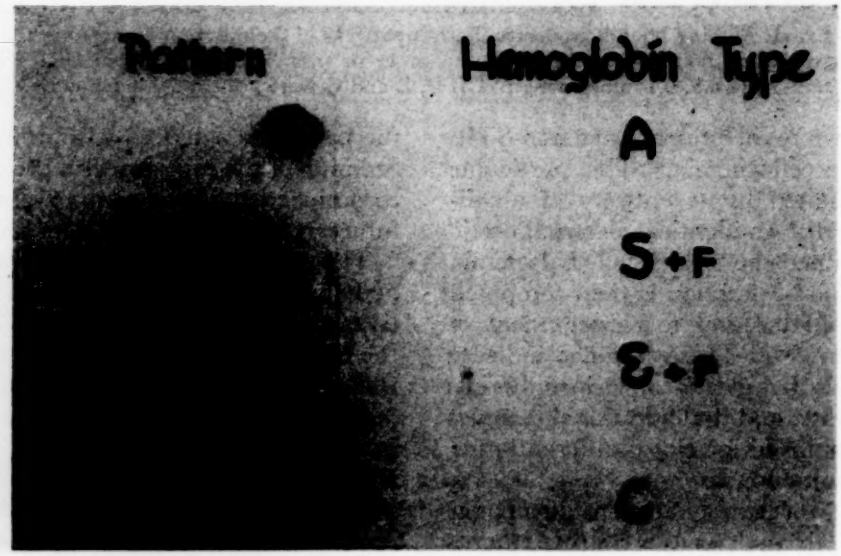

FIG. 3. Relative mobilities of Hb A, S, E and C (paper electrophoresis, pH 8.6). (We are indebted to Dr. A. I. Chernoff for the Hb E sample.)

assure maximal separation, and with the use of a densitometer, are still somewhat less exact than those obtained with the Tiselius apparatus.[45] "Tailing" of the compounds on the paper may also prevent recognition of smaller amounts of a component which may be distinctly differentiated by the moving boundary method.

2. Alkali Denaturation Technic. When oxy-Hb is exposed to alkali a brownish material—alkaline globin hematin[27]—is formed. The reaction involves oxidation of the heme iron to the ferric state as well as denaturation of the globin. The most important factors influencing this reaction are the pH, temperature and time of exposure. At pH 12.7 all the "non-resistant" Hb's are completely denatured within one minute.[9] If the exposure time is extended, the "resistant" Hb also will become partly denatured. Since all the nonresistant pigments are denatured within one minute, the "one-minute denaturation value" represents the percentage of alkali-resistant pigment minus the small quantity of this fraction (5 per cent) which has been destroyed during the performance of the test.

The total percentage can be computed from the one-minute denaturation value, corrected by addition of 5 per cent of this value.[28]

The method consists of exposing 0.1 cc. of an approximate 10 gm. per cent stroma-free hemolysate (which is also used for paper electrophoresis) to 1.6 cc. of N/12 NaOH for exactly one minute. The denaturation process is then interrupted by addition of 3.4 cc. of a reagent which precipitates the denatured chromogens and simultaneously stops the reaction by lowering the pH. This solution consists of 1 cc. of 10 N HCl added to 400 cc. half saturated ammonium sulfate. After filtering (Whatman No. 42), the unaltered Hb is determined in a photometer at 540 mμ. The Hb concentration of the filtrate, expressed as per cent of the initial amount of Hb used, represents the one-minute denaturation value.

In a study of over 1,000 specimens from normal adult persons, one-minute denaturation values of from 0.5 to 1.7 per cent have been obtained.[9,28] These readings are due to split products of the denatured proteins which go into solution and, possibly, also to minute amounts of "resistant" Hb present in adult blood. Values over 2 per cent definitely indicate the presence of an abnormal amount of alkali-resistant pigment.[9]

This "one point" denaturation technic is simple, rapid and very sensitive. Its main disadvantage is the indistinctiveness of the starting point which, however, is of little practical significance.

The method of determining the *total* amount of resistant Hb can be still more refined. The progress of the denaturation process is followed by permitting the alkali reagent to react with identical portions of the same Hb solution for intervals of increasing lengths of time and determining the remaining amounts of the unaffected pigment in these samples. By plotting the logarithms of these percentages against time, straight "lines of disappearance" are obtained which can be extrapolated to the ordinate (zero time).[10]

The denaturation process can also be followed directly in the spectrophotometer and the values plotted in the same fashion.[29,30] The latter method, however, has not given exact results below 7 per cent.[14] Thus the spectroscopic method seems to be less sensitive than the "precipitation" technic. White and Beaven[18] confirm the existence of an alkali-resistant Hb in various pathologic conditions. However, they find it less common than Singer et al.[9,28] since they take only values above 7 per cent into consideration. It will be shown that the demonstration of small amounts (below 7 per cent) of alkali resistant Hb may at times be of diagnostic significance.

Of the known Hb types, only fetal (type F) Hb exhibits resistance to alkali. Whether the alkali-resistant pigment fraction which appears in sickle cell anemia, thalassemia and other conditions is in all aspects identical with the similarly behaving compound found in cord blood, or whether it is only "fetal-like," remains a moot question.[9,31,32] At present it still seems most advantageous to designate any alkali-resistant human red cell pigment as Hb F.

3. Sickle Cell Tests, Tactoid and Gel Formation, Solubility Studies. In 1927 Hahn and Gillespie[33] discovered that distortion of susceptible erythrocytes into sickle cells will take place only if their Hb is in the reduced state. Presence of oxy- or carboxy-Hb prevents the sickling phenomenon. All tests for the demonstration of the sickling tendency are based on this behavior. Rapid sickling is obtained with agents which reduce the pigment at a fast rate, such as cultures of bacteria with a high oxygen consumption[34] or chemicals such as sodium dithionate ($Na_2S_2O_4$)[35] or sodium metabisulfite ($Na_2S_2O_5$).[36]

Sherman[37] noticed that sickle cells exhibit birefringence under the polarizing microscope. This finding indicates that the Hb molecules assume an orderly arrangement within the sickled erythrocytes.

After the discovery of type S Hb more detailed investigations of these fundamental observations became feasible. Perutz et al.[38,39] demonstrated that the solubility of reduced Hb S is about $\frac{1}{100}$ of that of the oxy-S-pigment, whereas reduced Hb A has about half the solubility of the corresponding oxygenated compound. Harris[40] found that hemolysates containing reduced Hb S become very viscous if the concentration of this pigment is at least 10 gm. per cent. With higher concentrations the formation of semi-solid gels was noted. Microscopic studies revealed the presence of birefringent "tactoids" in the viscous solution. Tactoids are boat- or spindle-shaped particles whose molecules have an orderly arrangement. The Hb S tactoids show a striking resemblance to sickled cells.[40,41] (Fig. 4.) It was therefore suggested that a sickled cell is in essence "a hemoglobin tactoid thinly veiled and somewhat distorted by the cell membrane."[40] Singer

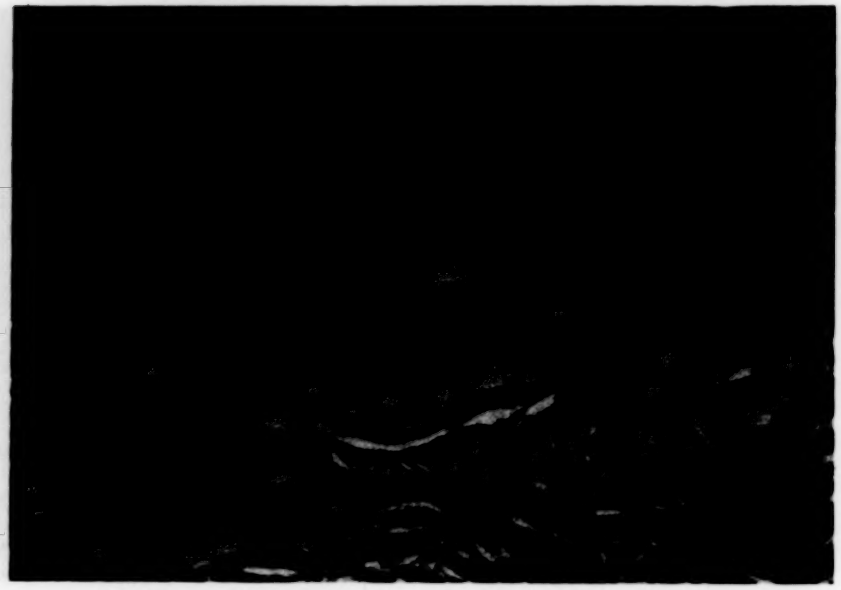

FIG. 4. S Hb tactoids (from Singer and Chernoff[41]).

and Singer[42] investigated hemolysates prepared from different types of S Hb containing erythrocytes in regard to their tendency to form gels. These erythrocytes carried variable amounts of A, C or F Hb in addition to the S pigment. The "lowest gelling point," defined as the minimal quantity of S Hb necessary for gelation, was determined for each of these Hb solutions. It could be shown that the lowest gelling points of hemolysates prepared from (1) erythrocytes of the sickle cell trait (containing Hb A + S), (2) from red cells of Hb C-sickle cell disease (containing C + S pigment) and (3) from erythrocytes of classical sickle cell anemia (containing Hb S + F) differ distinctly. It was then demonstrated that addition of Hb A decreases the amount of Hb S necessary for gel formation, and that Hb C reduces this amount still further. Hb F did not exhibit the property of interacting with the S pigment. If the sickling phenomenon is interpreted as being due to gel formation, and gel formation as being caused by polymerization of Hb S, Hb's A and C can act as co-polymers. The sickling phenomenon of sickle cell trait cells is thus produced not only by the presence of Hb S but also by its polymerization with the companion pigment (Hb A). The lowest gelling point of sickle cell trait hemolysates encountered was found to be at about 7 gm. per cent Hb S. With a mean corpuscular Hb concentration (MCHC) of about 34 ± 2 gm. per cent, the minimal percentage of Hb S required for a positive sickle cell test would be about 20 per cent, which corresponds to the lowest values found by electrophoresis in this condition. Should the Hb S concentration within the cells be less than 20 per cent, the sickling test may be negative although the abnormal Hb may still be demonstrable by the moving boundary technic. Such an observation has been described in genetic studies.[43]

The solubilities of the various types of Hb have been determined for the reduced compounds by Itano[6,44] and his findings have been essentially confirmed in the author's laboratory.[45] In Table II the pigments are grouped in the sequence of their solubilities. Solubility studies may be of practical significance for the differentiation between Hb D and S. These two pigments have identical electrophoretic mobilities; however, in the Hb D trait (in which the erythrocytes contain Hb A + Hb D) the sickle cell test is negative.[5,16,18] Reduced Hb D has a somewhat higher solubility than reduced Hb S.[6,44]

4. Spectroscopic Differences. Jope[46] discovered that human fetal Hb exhibits the so-called tryptophan-fine structure band at 2892 Å whereas Hb A reveals this band at 2910 Å. This difference, although small, has been successfully employed for the quantitative determination of Hb F.[4,18,47] The spectroscopic approach is, however, definitely less sensitive than the alkali denaturation technic since quantities below 10 per cent F pigment cannot be demonstrated in a mixture.[18] Except for the Hb M anomaly,[12] no other spectroscopic deviations have yet been observed for the abnormal pigment types.

In 1948 Hörlein and Weber[12] reported a

family in which met-Hb up to 24 per cent was present in the circulating blood of some members. Marked cyanosis was the only remarkable clinical feature. This anomaly was traceable through four successive generations, transmitted from one parent to some of the offspring and is therefore best explained genetically as representing a heterozygous condition. Spectroscopically, the met-Hb compound in these patients gave an absorption curve which differed from that of met-Hb prepared from normal adults. (Fig. 5.) Splitting off the heme from the protein moiety of the abnormal pigment, carefully avoiding denaturation, and recombining the abnormal pigment with hemes obtained from normal Hb, resulted in the re-appearance of met-Hb of the abnormal type. These findings strongly suggest the genetically conditioned existence of a specific abnormal globin moiety, for which the designation Hb M is proposed (see terminology). Search for this rare anomalous pigment should be undertaken in all instances of hereditary methemoglobinemia, especially since it seems evident from the literature that in some families with this syndrome the responsible gene behaves like a Mendelian dominant, whereas in others the genetic determinant acts like a recessive, requiring homozygosity for the appearance of clinical manifestations.[48]

5. Immunologic Differences. It is now well established that specific antisera can be obtained for Hb A and F.[49–51] These two pigments exhibit sufficient antigenic differences and share only a few antigenic groups, in contrast to Hb A and S which reveal a predominance of common antigenic factors, although a small number, specific for each pigment, has been demonstrated.[51] Chernoff[52] found small amounts of fetal pigment (up to 1 per cent) with a very sensitive quantitative technic in 70 per cent of normal adults. Ikin et al.[53] used cord blood erythrocytes for the immunization of rabbits. Specific sera were obtained which agglutinated not only the erythrocytes of newborns but also abnormal erythrocytes known to harbor F Hb, such as the red cells in sickle cell anemia and in thalassemia.[54] Thus the similarities of the F pigment in these conditions are also demonstrable by the immunologic approach.

6. Other Differences between the Hemoglobin Types. (Table II.) Perutz et al.[39] compared the x-ray diffraction patterns of crystals of Hb A and S and found them to be identical. This observation is of great significance if it is realized that x-ray analysis of Hb's from even very closely related animal species show totally diverse patterns. On this account no great *structural* dissimilarities can be expected to exist between these two Hb types despite their dissimilarities in electrophoretic behavior and in solubility.

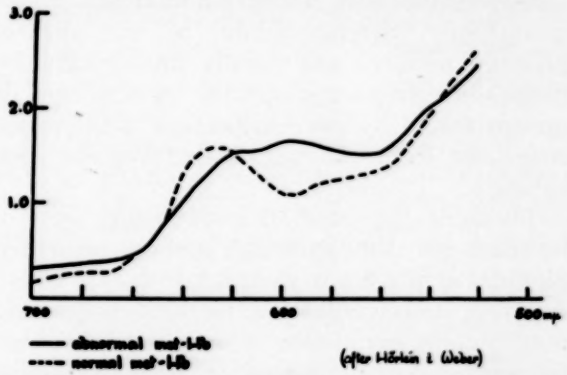

FIG. 5. Absorption curves of abnormal and normal met-Hb.

Analysis of amino acid composition of Hb's A and S showed only slight and probably insignificant discrepancies[55] but revealed several more marked differences in the fetal pigment;[31,56] for example, the isoleucine content of Hb A amounts to 0.4 gm. per cent but that of Hb F is 1.4 gm. per cent. Determination of the terminal amino end groups of the globins by tagging them with dinitrofluorobenzene (Porter and Sanger[57]) showed identical results for Hb A, S and C.[57–59] The terminal amino acid was identified as valine. Valine was also found to be the terminal amino acid in fetal Hb but quantitatively only about half the value was found for F Hb as compared with the adult pigment.[57] Other differences of the Hb types in regard to free SH groups[60] and free carboxyl groups,[61] as far as they have been investigated, are listed in Table II.

The dissimilarities in the various human pigments are considered at present to be caused essentially by differences in the folding and coiling of the polypeptide chains which constitute the globin molecule.[3,55] Since the Hb abnormalities are genetically controlled, one must visualize the specific gene action as directing these particular aspects of globin synthesis.

CLINICAL HEMOGLOBIN ANALYSIS

Performance of paper electrophoresis at pH 8.6 in combination with the alkali denaturation technic will suffice to uncover almost any of the Hb abnormalities so far described. If the

presence of Hb D is suspected solubility studies may be helpful. It is suggested that the various components demonstrated in hemolysates be reported in the sequence of their quantitative representation.[28] Thus the formula S + A + F indicates that Hb S is the major and Hb A the larger of the two minor components. Exact quantitative determinations of the electrophoretic patterns are usually unnecessary for diagnostic purposes since the results can be approximated by mere inspection of the paper strip and from the one-minute denaturation value.

Theoretically, some Hb abnormality can not be ruled out if the mobility of the investigated pigment at pH 8.6 is identical with that of Hb A. It is conceivable that mobility differences may become manifest only at lower pH values. In case of doubt, aroused by unusual clinical features, complete characterization of a pigment compound by *all* available technics is desirable and may occasionally be rewarding.

GENERAL GENETIC ASPECTS OF THE DISEASES ASSOCIATED WITH ABNORMAL HEMOGLOBINS

The assumption that the determinants for pathologic Hb types are alleles of the genes for Hb A provides the most satisfactory explanation of the basic genetic features of these diseases.[62–66] Since, however, the expressivity of the abnormal genes varies markedly from individual to individual, the influence of modifying genes must also be postulated.[64] With the possible exception of the thalassemia gene, these modifiers have not yet been identified.[67] Furthermore, the irregular appearance of considerable amounts of F Hb in homozygous or double heterozygous conditions, such as sickle cell anemia, Hb C + S disease, Hb S, (or C, or E)—thalassemia disease, and the "pure" thalassemic syndromes, poses another difficult problem which cannot longer be ignored.[23] It has been postulated (1) that Hb F production is also controlled by genes which, however, are *not* alleles of those for Hb A; (2) that the activities of the F Hb genes are almost completely suppressed by the genes for Hb A in the post-infancy period; and (3) that this suppression becomes less complete if certain pathologic gene combinations exist which result in Hb and/or red cell structure anomalies.[23]

DISORDERS ASSOCIATED WITH HEMOGLOBIN S

Sickle cell disease is the generic term applied to all disorders associated with red cells carrying S pigment.[68] A positive sickle cell test merely proves the presence of S Hb. Hb analysis, however, permits a sharp classification of these syndromes on an objective basis. The following variants of sickle cell disease can be distinguished.

1. The sickle cell trait (sicklemia) is characterized by the A + S pattern (Figs. 1 and 2) and represents the heterozygous state for the Hb S gene. The amount of S pigment varies from about 50 to 20 per cent of the total Hb[28,69,70] and may even be less in exceptional instances.[43] Attempts have been made to trace the genetic modifiers responsible for the variable expressivity of the S Hb gene in family studies.[70] Persons with the Hb S trait reveal no other hematologic abnormality referable to the pathologic Hb. The survival time of the "trait" erythrocytes is within physiologic limits (about 120 days[71,72]); this is of great practical importance since trait carriers can be used as donors for transfusions like any normal person. Although most individuals with the A + S pattern remain clinically asymptomatic, some tend to develop vascular occlusions. Gross, painless hematuria, leading at times to severe anemia and necessitating nephrectomy, has been repeatedly observed.[73] Plugging of smaller renal vessels by elongated sickled cells, venous stasis and parenchymal necrosis are seen histologically. Cerebral thrombosis and/or other vascular obstructions may be encountered following high altitude flying, or in the course of mountain climbing.[45,73–75]

Incidence. About 9 per cent of the American Negro population harbors the sickle cell trait.[76] Its incidence in Africa varies from tribe to tribe and may be as high as 45 per cent.[73,77] Sickling has also been found in India[78] and in Europeans of Greek[79] or Italian[80] extraction. Whether these observations may perhaps suggest that the Hb S gene is not necessarily a Negroid characteristic is not clear.

2. Sickle cell anemia, as proven independently by Beet[81] and by Neel,[64,76] represents the homozygous state for the Hb S gene. However, only rarely is Hb S the sole component in the hemolysate. Usually a non-S fraction is demonstrable which varies from 2 to 24 per cent (see Table III and Figures 1 and 2) and is entirely composed of alkali-resistant F Hb.[9,20] The S, or the S + F pattern is therefore characteristic of this syndrome. The percentage of F Hb may fluctuate considerably (from 18 to 8 per cent) over longer periods of time in the same person

for no apparent reason.[45] Jonxis[32] stated recently that the alkali-resistant fraction does not reveal the high isoleucine content characteristic of cord blood F Hb, and assumes that this pigment is fetal-like.

TABLE III
PERCENTAGE OF F HB, AS DETERMINED BY THE ALKALI DENATURATION TECHNIC,[9] IN EIGHTY PATIENTS WITH SICKLE CELL ANEMIA*

Per cent F Hb	No. of Cases
21–25	3
16–20	5
11–15	15
6–10	20
2– 5	33
below 2	4

* For practical purposes, good agreement exists between the non-S Hb fraction determined electrophoretically and by the alkali denaturation technic.[20]

Surprisingly, the S and F pigments are not evenly distributed within the red cell population.[82] From the different disappearance rates of the erythrocytes and of the alkali-resistant Hb following transfusion of sickle cell anemia blood into normal recipients, it has been concluded that the red cell population is composed of three main portions, (1) red cells containing predominantly S and no or only little F Hb, (2) cells containing both pigments and (3) cells containing predominantly F and no or only little S Hb.[82] The "F" cell portion has the relatively longest survival time which is, however, still considerably shorter than that of normal erythrocytes.[82]

Hematologic Features.[73,83] Nearly all patients have a normochromic normocytic anemia with Hb levels averaging about 7 to 9 gm. per cent although lower or slightly higher values may be encountered. The anemia is hemolytic in nature, as evidenced by the shortened survival time of the erythrocytes (fifteen to sixty days).[71,72] The hemolytic syndrome is of the "intracorpuscular" variety:[84] normal erythrocytes, transfused into the patient, survive normally. As might be expected, erythrocytic hyperplasia of the marrow, high reticulocyte output, hyperbilirubinemia without bilirubinuria and an elevated hemolytic index are found.[84] Leukocytosis and thrombocytosis are also present. The film shows numerous sickle cells, target cells, basophilic stippling and, irregularly, nucleated red cells. The osmotic fragility of the erythrocytes is decreased. Sherman[37] demonstrated intravascular sickling, ranging from 30 to 60 per cent in venous blood which was obtained avoiding exposure to oxygen. Less than 1 per cent sickled cells was found in the sickle cell trait.

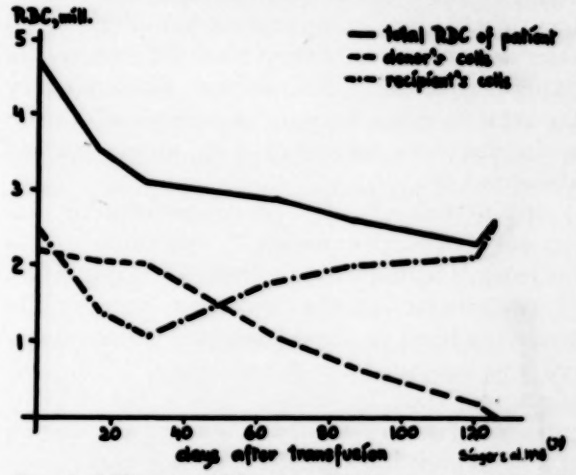

FIG. 6. Influence of blood transfusions on the red cell population in sickle cell anemia.

A remarkable reaction to large blood transfusions is observed in sickle cell anemia. If the patient's circulation is repleted to normal values for red cells and Hb, the erythrocytic hyperplasia of the marrow disappears, the reticulocyte output ceases, but the accelerated elimination of the patient's own erythrocytes continues unaltered.[45,71,85] Red cell production is resumed if the number of "foreign" normal erythrocytes decreases sufficiently, and after their complete disappearance the status quo is reached again.[71] (Fig. 6.) If a normal Hb level is maintained by repeated transfusions over a longer period of time the patient's own red cell production remains almost completely suppressed.[45] A similar suppression of the red cell output has also been achieved by breathing of high oxygen concentrations over longer time intervals.[86,87]

Crosby and Akeroyd[88] have recently emphasized the distinction between compensated hemolytic processes and hemolytic anemias. If the rate of red cell disintegration is six to eight times that of normal (*average* survival time of about fifteen to twenty days), no anemia may be present since the functionally normal marrow is capable of compensating for this increase in elimination rate by an increase in red cell delivery. Anemia will result if the rate of erythrocyte disintegration exceeds this limit, or if the

marrow cannot maintain this necessary overproduction. In sickle cell anemia this regulatory mechanism is severely disturbed. The marrow "thermostat" is set at a lower level. If this level is reached, erythrocytogenesis ceases.[45] On account of this peculiar disturbance of the regulatory mechanism, compensated hemolytic processes are not, or only very rarely,[89] observed in patients with the S + F pattern, although they are seen in other variants of sickle cell disease or in disorders associated with other types of abnormal Hb.

Aplastic Crises.[90] In the course of acute infections (virus pneumonia,[90] infectious mononucleosis,[91] Salmonella choleraesuis[91]) inhibition of erythrocyte production may occasionally occur resulting in almost complete cessation of red cell output from the marrow.[90,92,93] This effect may last for about two weeks. Absent entrance of new erythrocytes into the circulation of a *non-anemic* individual for such a period will cause only a slight decrease of the red cell count.[93] In a patient with a hemolytic syndrome it may have serious consequences: a precipitous fall in the erythrocyte and Hb levels within a few days may take place due to the markedly shortened life span of the circulating red cells. This mechanism was first elucidated by Owren[92] in hereditary spherocytosis, and was found to apply also to sickle cell anemia.[93] When one of our patients with homozygous Hb S disease contracted virus pneumonia, a 50 per cent diminution of his red cell count occurred within three days. Several months later, after complete recovery from the infection, the patient's red cells were transfused into a normal recipient; again 50 per cent of his erythrocytes disappeared within three days, the remainder being eliminated within the following twenty-five days.[90] Thus different portions of the red cell population exhibit different survival times.

It would indeed be intriguing to demonstrate unequivocal correlations between the life spans of various portions of the red cell population and their S and F Hb contents. But the situation is not so simple. Comparative survival time studies of the erythrocytes from two individuals, both containing almost only S Hb, revealed marked life span differences between their cells when transfused into the same recipient.[45,82] The sickle cell pigment is therefore not the only factor governing red cell survival in this disorder. Other anomalies, not yet recognized, may also contribute to the shortened life span of these erythrocytes.

Clinical Features. The symptomatology[73,83] of sickle cell anemia is not confined to hematologic alterations; the function of almost any organ of the body may be affected. Such disturbances are either a sequel of the chronic hemolytic anemia, or are produced by vascular obstructions due to sickled cells, or may be caused by a combination of both mechanisms. Space does not permit a detailed discussion of the variegated clinical picture;[73,83] only the principal features will be enumerated: (1) Thromboses of various cerebral vascular areas are responsible for many neurologic signs; (2) tortuosity of the retinal vessels are noted; (3) cardiomegaly, associated with systolic and diastolic murmurs, arrythmias, a prolonged P-R interval, may lead to the wrong diagnosis of rheumatic heart disease which seems to be supported further by complaints of (4) frequent nosebleeds and (5) intermittent episodes of severe arthralgia. (6) Hepatomegaly is common and liver function tests may reveal considerable parenchymal impairment.[94] (7) The spleen is enlarged in younger individuals although, with advancing age, thromboses of the splenic vessels bring about fibrosis of this organ (autosplenectomy). We have observed several instances of sudden splenic vein thrombosis associated with severe thrombocytopenic purpura, which disappeared after splenectomy. (8) Gallstone formation is not rare, as in most chronic hemolytic syndromes. (9) Hematuria, similar to the syndrome observed in the sickle cell trait, may be present. A nephritic syndrome with azotemia has been described. Priapism, due to obstruction of the corpora cavernosa, is a painful event. (10) Torpid skin ulcers of the lower extremities are frequently seen and are more common in adults. Pregnancy may enhance their healing in a manner not yet understood.[45,96] (11) Severe bone changes, such as the "hair-on-end" appearance of the skull and cupping of the vertebrae are not specific and occur in chronic anemias associated with marked marrow hyperplasia.[12] The so-called "abdominal crisis," a term denoting attacks of severe abdominal pain, may closely simulate an acute surgical condition of the abdomen. Such a "crisis" may last for a few days and may recur at variable intervals. Some patients with classical sickle cell anemia, however, never experience them.[45] The mecha-

nism responsible for these attacks is not yet understood. Vascular occlusions have been accused. Contrary to a widespread belief, the "abdominal crises" are not associated with an increase in hemolytic activity.[45,97]

Prognosis and Treatment. Patients with sickle cell anemia are particularly prone to intercurrent infections. Treatment with antibiotics and transfusions has reduced the mortality rate in this disease and more patients reach the fourth and fifth decade of life. Transfusions for correction of the anemia are indicated if the Hb level decreases dangerously, as during an aplastic crisis or due to other complications. They may be given prophylactically in pregnancy complicated by sickle cell anemia at the start of labor. Massive blood transfusions may also bring about healing of skin ulcers[45,95] resistant to local therapy. Although prognosis in regard to life expectancy has improved, no specific treatment for sickle cell disease is yet available. ACTH and cortisone have proved valueless. Splenectomy exerts no influence but may be of value in superimposed thrombocytopenic purpura due to splenic dysfunction. Many but not all patients with sickle cell anemia lead the life of "hematologic cripples." The abdominal crises require symptomatic treatment with sedatives, analgesics and sometimes narcotics. Recently, priscoline® has been reported to give dramatic relief.[144] Other clinical manifestations which are not specific for sickle cell disease, such as congestive heart failure, hematuria, priapism, are treated in the usual established manner.

Incidence. The incidence of sickle cell anemia in the United States Negro population has been estimated to be 0.22 per cent.[76] In Africa one would expect to find a much higher incidence but the opposite appears to be the case. This has been attributed to the excessively high mortality rate in childhood in these regions.[77]

3. Hb C—sickle cell disease represents the double heterozygous state for these two abnormal Hb's.[63,98] Hb analysis reveals the C + S or C + S + F pattern; occasionally the combination S + C has also been encountered.[99] In our own series of seventeen patients the C pigment varied from 67 to 50 per cent.[45] F Hb is irregularly present (up to 8 per cent).

Hematologically, either a compensated hemolytic process or a mild anemia exists. The MCV and MCH are either normal or decreased, the MCHC is usually normal. The reticulocyte output is elevated to compensate for the variably shortened life span of the erythrocytes. In the film, the number of sickle cells is scarce but target cells are very conspicuous (50 per cent or more). Intravascular sickling was always demonstrable in our patients (3 to 15 per cent), although much less than in homozygous Hb S disease.[45]

The *non-hematologic* symptoms and signs are as a rule much milder than in classical sickle cell anemia and many patients are not even aware of their condition. Hepatomegaly, more or less marked splenomegaly, ocular and renal hemorrhage, and priapism have been noted in our series of unselected patients but most come to the hospital for unrelated diseases. On the other hand, Smith and Conley,[89] re-examining atypical cases of sickle cell disease, emphasize that the C + S syndrome may at times cause much more severe symptoms. They observed abdominal crises, aseptic necroses of the humoral and femoral heads, stepped-up hemolytic activity during pregnancy, and other severe clinical features usually seen in true sickle cell anemia only. Again, no direct correlation is demonstrable between the individual severity of the clinical manifestations and the quantitative results of Hb analysis. In the past physicians having observed such milder cases of "sickle cell anemia," have frequently speculated on transitions between the "trait" and the "anemia." No such transitions exist, however; the milder cases belong to now recognizable variants of sickle cell disease.

4. Hb S—thalassemia (microdrepanocytic) disease represents the double heterozygous state for the S Hb and the thalassemia genes.[21–23,80,100] The latter has been proven by Silvestroni and Bianco[80] *not* to be an allele of the Hb genes, since (1) the offspring of parents, one of whom had microdrepanocytic disease and the other thalassemia, were normal and, (2) a child of parents, one with microdrepanocytic disease and the other normal, also had microdrepanocytic disease. Typically, Hb analysis shows the S + A + F or the S + A pattern.[23] The electrophoretic findings are indistinguishable from those in sickle cell anemia but the values obtained with the alkali denaturation procedure reveal the non-S Hb fraction to be predominantly or exclusively composed of Hb A.[23] Occasionally, however, when the F Hb values are high, the distinction cannot be made with certainty and then only genetic studies and the hematologic features may

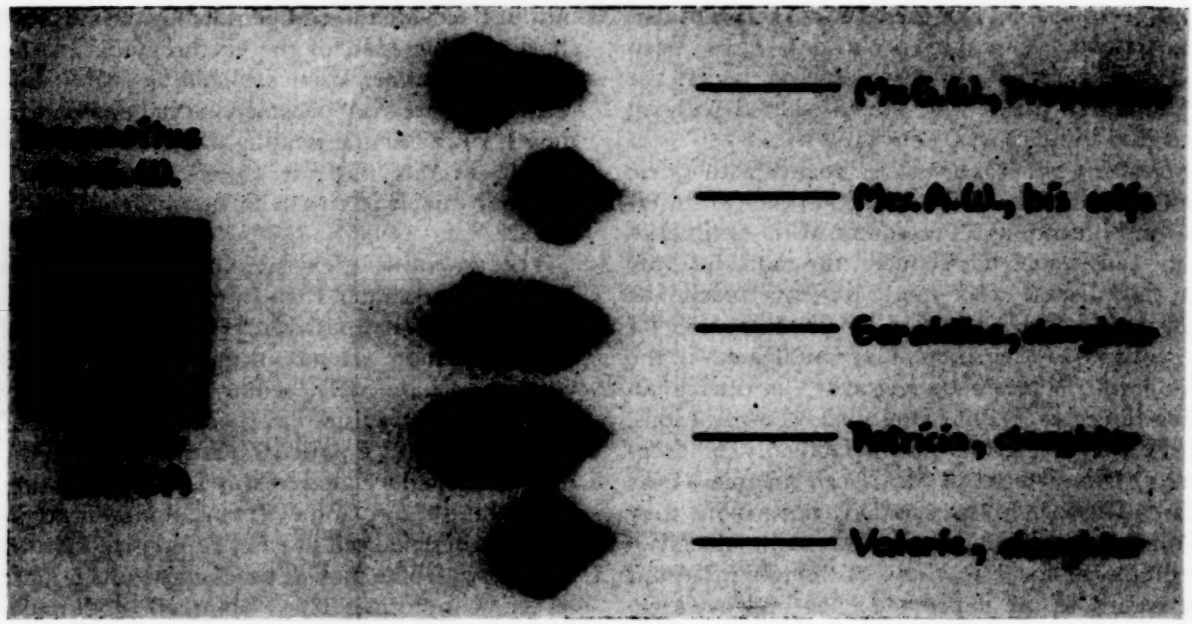

FIG. 7. Electrophoretic patterns in sickle cell-thalassemia disease. The propositus G. W., a thirty-five year old male Negro, shows 5 million red blood cells, 12.5 gm. per cent Hb and 3.1 per cent reticulocytes. The MCV is 80, the MCH 25 and the MCHC 31.3. Physical examination was essentially negative. He had been considered a carrier of the sickle cell trait in several hospitals. Although this patient has a high percentage of S Hb, he is heterozygous for the S Hb gene since one daughter of his marriage to a hematologically normal person is also normal.

help in differentiating Hb S—thalassemia disease from sickle cell anemia.[45,89] Although 60 to 80 per cent of S Hb is present in the hemolysate, the patient is heterozygous for the abnormal Hb gene. A similar high percentage for the abnormal Hb has been observed in the analogous conditions of Hb C— and Hb E—thalassemia disease.[67,101] To explain this fact it has been postulated that the thalessemia gene modifies (enhances) the expressivity of the pathologic Hb gene;[67] another hypothesis suggests that the synthesis of Hb A, but not of the abnormal Hb's, is impaired in thalassemia.[47] Interestingly, in microdrepanocytic disease not all the erythrocytes appear to carry S Hb when examined with the polarizing microscope;[102] the distribution of the various pigments is therefore an uneven one, similar to the previously mentioned findings in classical sickle cell anemia.[82]

Hematologically, both the features of sickle cell anemia and of thalassemia may be observed. The hemolytic anemia is definitely microcytic as evidenced by a low MCV and MCH, but the MCHC is either normal or only slightly decreased. Compensated hemolytic processes are, however, also encountered.[23] In the film, sickle cells are fewer in number but target cells are more conspicuous than in sickle cell anemia. The *non-hematologic* manifestations show all transitions from the severest clinical features described in sickle cell anemia to an almost asymptomatic state.[23,80] Although most reports on this variant of sickle cell disease deal with individuals of Greek or Italian descent, the disorder has recently been shown to occur not infrequently in the American Negro.[23,103,104] If the clinical manifestations are mild and no Hb analysis is performed, such patients may be classified erroneously as carriers of the sickle cell trait. (Fig. 7.)

5. Hb D—sickle cell disease represents the double heterozygous state for these two abnormal pigments. Since Hb D has the same electrophoretic mobility as Hb S, its recognition is supported by solubility studies.[5,44] Amounts up to 12 per cent F Hb have been found in Hb D + S disease.[16] Discovery of the Hb D component usually comes from genetic investigations. The electrophoretic pattern of the A + D trait is found in relatives of patients afflicted with Hb D + S disease. The Hb A + D trait gives a negative sickling test although electrophoretically it is indistinguishable from the sickle cell trait.[5]

The clinical manifestations are those of a moderately severe hemolytic syndrome. Only two unrelated families exhibiting this disorder have so far been observed, one in the United

States.[5,105] and one in England.[18,106] The remarkable feature of this rare condition is its occurrence in individuals of *apparently* Caucasoid origin. Even if one postulates that Hb D is a Caucasoid characteristic, it is still amazing that Hb D + S disease has been reported in whites only. The Hb A + D trait is clinically asymptomatic.

6. Other Variants of Sickle Cell Disease. Simultaneous occurrence of the sickle cell trait with hereditary spherocytosis has been observed in one patient[89] but a detailed description of this syndrome is not yet available. Combinations such as homozygous Hb S + thalassemia disease (resulting from the marriage of a patient with microdrepanocytic disease and a carrier of the sickle cell trait), or Hb C + S + thalassemia as well as the association of Hb E or Hb G with sickle cell disease are predictable but have not yet been reported.

Special Genetic Aspects of Sickle Cell Disease. It has been pointed out that the incidence of the S Hb gene in Africa may be as high as 45 per cent but that sickle cell anemia is relatively rare due to the high mortality rate of sickle cell anemia patients in childhood. This has raised the baffling problem how, in the presence of such a marked gene loss, so high a percentage of sickle cell carriers can be maintained. An extremely high mutation rate or a tremendous increase in fertility would have to be assumed to explain this phenomenon.[64] Both explanations do not seem satisfactory. Beet,[81] and recently particularly Allison,[73,107] have emphasized that carriers of sickle cells are less prone to succumb to tropical malaria. If this is true the abnormal S Hb provides a selective advantage, and the proportion of individuals with sickle cells in any population will be the result of a balance between the severity of malarial infections (which will tend to increase the frequency of the gene) and the rate of elimination of the sickle cell genes in individuals dying from sickle cell anemia.[107] This results in a "balanced polymorphism" in which the heterozygotes for S Hb have an advantage over both homozygous A or homozygous S individuals.[107] The relatively low incidence of 9 per cent of the sickle cell trait in the United States versus the higher incidence of about 20 per cent in West Africa—the supposed origin of the American Negro—may thus be explained as being due to the rare occurrence of malaria in the United States. One might expect progressive decrease in the sickling frequency in the American Negro in the future which, however, would then be counterbalanced by the decreased mortality and increased fertility rates of patients with sickle cell anemia due to better medical care. Many more investigations on the interrelationship of malaria and Hb S are needed before this interesting interpretation can be fully accepted.

DISORDERS ASSOCIATED WITH HEMOGLOBIN C

Target cells are almost regularly observed in all disorders associated with Hb C[63,98,108,109] but are not specific for the presence of this pigment. The causative interrelationship between Hb C and this erythrocyte shape anomaly is not yet understood. Marked "targeting" in a Negro patient is a definite indication for Hb analysis. The following conditions associated with Hb C have so far been recognized.

1. The Hb C Trait represents the heterozygous state for this abnormal pigment. Hb analysis shows the A + C pattern, the percentage of C Hb varying from 28 to 40 per cent.[4,28,44,45] No hematologic abnormalities are present except for a variable degree of leptocytosis, which may be associated with a decreased osmotic fragility. Most carriers of the C Hb trait are asymptomatic but intermittent arthralgia is a frequent complaint.[45,110] The incidence of the Hb C gene in the American Negro amounts to about 2 to 3 per cent;[25,45,99] in West Africa, however, it was found to be as high as 12 per cent.[111]

2. Pure Hb C Disease. In the homozygous state for Hb C this pigment is usually the sole component found in the hemolysate.[109,112–115] However, on the African Gold Coast up to 14 per cent of F Hb has been reported in this condition.[111] *Hematologically*, a compensated hemolytic process or a mild anemia is found. Leptocytosis is very conspicuous and the osmotic fragility is markedly decreased. The survival time of the red cells is diminished[109,115] to about fifty days and with the Ashby technic a distinct heterogeneity of the red cell population may be demonstrable. About 20 per cent of the transfused erythrocytes were noted to survive considerably longer than the others.[115] Such observations may suggest the existence of other intra-erythrocytic defects besides the abnormal Hb. Since in the anemic cases the average survival time is *not* markedly shortened, a relative inability of the marrow to compensate for the accelerated rate of erythrocyte disintegration

may be a contributing mechanism.[110] Splenomegaly is almost regularly found and may be very marked. Splenectomy does not ameliorate the hemolytic process.[115] Episodes of joint and bone pains have been noted. Pure Hb C disease has so far been reported in one white individual of Italian descent;[143] its incidence in the American Negro has been estimated to be 1 in 6,000.[110]

3. Hb C—thalassemia disease represents the double heterozygous state for the Hb C and the thalassemia genes. Two Negro patients with this syndrome have been observed in the author's laboratory.[67] Hb analysis showed the C + A and the C + A + F patterns, with Hb C amounting to about 75 per cent. Both patients had a microcytic erythrocytosis (6 million) with low MCV and MCH but normal MCHC. The reticulocyte output was slightly elevated. Half of the red cells were target cells and the osmotic fragility was definitely decreased. No hepatosplenomegaly was observed. Other family members suffered from a severe thalassemic syndrome or exhibited the Hb C trait. The interaction of the Hb C and the thalassemia genes did not produce a severe clinical syndrome in these instances. As mentioned in the discussion of Hb S—thalassemia disease, the high percentage of the pathologic pigment in the hemolysates may be attributed to the modifying effect of the thalassemia gene. Zuelzer and Kaplan[116] also have reported the simultaneous occurrence of Hb C and thalassemia but did not notice this increase of the Hb C percentage. Their patient showed a marked anemia (6.8 gm. per cent) and the MCV and MCH of the erythrocytes were considerably decreased. In the film many target cells were seen, as well as extreme pleomorphism of the red cells in association with some microspherocytes.

This discrepancy in the hematologic manifestations of individuals heterozygous for both Hb C and thalassemia suggests entirely different types of "gene interaction." The complexity of the latter may not always be reflected in the results of Hb analysis.

4. Hb C—sickle cell disease has been commented upon in the section on sickle cell disease.

HEREDITARY DISORDERS ASSOCIATED WITH HEMOGLOBIN F

Hb F constitutes 50 to 90 per cent of the red cell pigment in the newborn.[19,117–119] Within the first seven to twelve months of life it is usually replaced by Hb A or, in the hemoglobinopathies, by the respective abnormal pigments. However, small amounts (less than 5 per cent) may continue to be demonstrable in *some* normal children up to school age[119,120] and immunologic procedures have detected persistence of minute amounts in adults.[52] Hb F production does not cease abruptly after delivery and is not confined to extramedullary hematopoiesis.[119] No convincing evidence is available that F Hb is, at least *in vivo* a functionally "better" Hb than Hb A.

Hb F has been detected in some of the thalassemic syndromes,[9,12] in some patients with hereditary spherocytosis[9] and in the previously discussed disorders associated with pathologic Hb's.

1. The Thalassemic Syndromes: (Mediterranean hemopathic syndromes,[122,123] Mediterranean anemia[124], hereditary leptocytosis,[125] Cooley's anemia.[126]) It is now well recognized that thalassemia manifests itself as a group of hereditary syndromes, showing all sorts of gradations from the most severe Cooley's anemia to the asymptomatic "trait."[123,124,127–129] The common denominator of these disorders is the production of structurally defective, thin (leptocytic) erythrocytes which exhibit this anomaly to a varying degree in various patients. For practical purposes we have found the following classification based on alterations of the red cell and Hb levels,[67] very useful. (1) Thalassemia major (Cooley's anemia): very severe microcytic hemolytic anemia; (2) thalassemia intermedia: less severe but still marked anemia; (3) thalassemia minor: mild anemia; (4) microcytic erythrocytosis; and (5) thalassemia minima: slight leptocytosis only. Valentine and Neel[130] have suggested that thalassemia major represents homozygosity for a genetic factor which is heterozygous in the other syndromes, grouped together by these authors as "thalassemia minor." These investigators were aware of the varying expressivity of the thalassemia gene, due to modifying factors in the heterozygotes, but considered markedly anemic (intermediate) types as being of very rare occurrence. With increasing experience the more severe "minor" types of thalassemia have been seen more frequently and doubt has been expressed whether these intermediate forms are always heterozygous.[67,123] Be that as it may, there is general agreement that mating between any of the thalassemic types may result in offspring with homozygous Cooley's anemia.[130]

Hb analysis has revealed high values (40 to

almost 100 per cent) Hb F in thalassemia major[47,121,131] and none in thalassemia minima.[9] In thalassemia intermedia F Hb is quite regularly present (20 to 40 per cent[67]). In thalassemia minor and in microcytic erythrocytosis, it may or may not be detectable.[9,67] Since thalassemic syndromes of the same apparent severity exhibit markedly different F Hb percentages, it is not clear whether *any* pathogenetic significance can be attributed to its presence. It has been speculated that the thalassemia gene renders the postulated physiologic suppression of the F Hb genes less complete.[23] Another hypothesis considers that the synthesis of Hb A is impaired to a variable degree in this disease, and substitution by the production of F pigment takes place.[47]

Hematologic Features. Although the typical thalassemic erythrocytes have a low MCV and MCH, the MCHC is much less diminished, in the milder forms not at all.[67,123] Varying with the severity of the disturbance, anisocytosis, poikilocytosis, schistocytosis, ovalocytosis and basophilic stippling, as well as target cells, are more or less conspicuous. The osmotic fragility is always decreased and in thalassemia major may be altered to such an extent that some of the erythrocytes cannot be hemolyzed even by distilled water. Although leptocytosis is a basic feature of the thalassemic erythrocytes, the alterations responsible for this shape anomaly remain unknown. It is quite likely that the leptocytosis seen in disorders associated with Hb C is fundamentally quite different from the leptocytosis caused by the thalassemia gene. But these differences cannot yet be formulated in biochemical terms.

The erythrocyte population in Cooley's anemia shows a heterogenous composition.[133] About 20 to 50 per cent of the erythrocytes are rapidly eliminated but the remainder have a normal life span. In the milder syndromes the life span of the red cells may be within normal limits.[133,134] Since normal erythrocytes transfused into patients with thalassemia frequently exhibit a normal life span, this hemolytic syndrome belongs to the "intracorpuscular" category.[133] However, in *some* patients an extracorpuscular mechanism exists simultaneously, as evidenced by the rapid elimination of transfused normal cells, and in these instances splenectomy may be beneficial.[135] Fluctuations in red cell delivery have been observed[136] and the effect of large blood transfusions in suppressing erythrocytogenesis is analogous to the situation described in sickle cell anemia.[45] Although more investigations are still needed, one cannot avoid the impression that the more severe disorders associated with abnormal Hb's and with thalassemia reveal the features of dyserythropoiesis (faulty regulation of red cell production and delivery) as well as hyperhemolysis of the defectively constructed cells.

Other clinical manifestations,[83] which are usually noticeable only in the more fully developed syndromes, are (1) Mongoloid facies, (2) hepatosplenomegaly, which may be very marked in thalassemia major and barely noticeable in thalassemia minor or thalassemic erythrocytosis, (3) bone changes similar to those mentioned in sickle cell anemia, (4) leg ulcers and (5) a tendency to gallstone formation.

Prognosis and Treatment. Cooley's anemia is a disorder starting early in infancy and requiring frequent blood transfusions for maintenance of life; it usually terminates fatally within a few years. Severe thalassemic syndromes, classified as intermediate types have, however, been observed in adults and are compatible with a long life span.[123] No specific treatment is available. Iron medication is ineffective. The irregular improvement of thalassemia major by splenectomy has been mentioned. Massive blood transfusions, establishing a normal Hb level and maintaining it over a longer period of time, may bring about healing of torpid leg ulcers.[45] When the transfused erythrocytes are completely eliminated the ulcerations may not recur.

Occurrence and Incidence. Thalassemia is a common disease in some Mediterranean countries (Italy, Greece, Syria). Further studies, however, have revealed that "Mediterranean anemia" is also frequently found in other parts of the world: in India,[137] Thailand[138] and Indonesia.[139] It has been seen in Chinese[125] and also in the American Negro.[67,140] Thus the term "Mediterranean" anemia does not seem to be appropriate; for want of a better designation, which should be related to the basic as yet unknown erythrocytic defect, we prefer the term "thalassemia."

Neel and Valentine[141] estimate the incidence of thalassemia minor as one in twenty-five persons, and of thalassemia major as 1 in 2,368 births in the large Italian population in Rochester, N. Y. The maintenance of the high frequency of the thalassemia gene poses the same

puzzling problem as previously pointed out for the sickle cell gene. Whether the thalassemia gene provides any selective advantage to its carriers is not yet clear.

2. Hereditary Spherocytosis. Occasionally, patients with hereditary spherocytosis may show Hb F up to 8 per cent[45] in their hemolysates.[9] Although the anemia disappears completely after splenectomy, the production of F Hb continues unaltered. This finding supports the interpretation that F Hb production in these instances may be genetically controlled. Why F Hb is found only in some patients is not understood.

DISEASES ASSOCIATED WITH HEMOGLOBIN E

Minnich et al.[138] noted a high incidence of severe thalassemic syndromes in Thailand. Genetic analysis instigated further investigations which demonstrated the presence of Hb E in some of these patients. Chernoff, Minnich et al.[101] have recently published preliminary data on the diseases associated with this abnormal pigment. The following three variants have been recognized:

1. The Hb A + E trait: Carriers of this Hb anomaly are clinically asymptomatic.

2. Pure Hb E disease represents the homozygous state for this pathologic pigment. Small amounts (up to 6 per cent) of F Hb may be present besides Hb E. Hematologically, microcytosis and numerous target cells (25 to 60 per cent) as well as a symmetric shift of the osmotic fragility curve to the right are noted in these patients who may also show hepatosplenomegaly, arthralgia and jaundice.

3. Hb E—Thalassemia Disease. Hb E comprises 60 to 80 per cent of the total Hb, the remainder being F Hb. The symptomatology is hematologically and clinically almost indistinguishable from thalassemia major, although the course is somewhat milder. The majority of the patients live to adulthood. The osmotic fragility curve is asymmetrically shifted to the right.

Incidence. The incidence of the "Mongoloid" Hb E in Thailand was found to be 12.5 per cent. Since it is now evident that thalassemic syndromes may be associated not only with Hb F but also with Hb S, or C, or E, the older literature on this disease needs re-evaluation. Hb analysis has become a necessary requirement for delineation of these disorders.

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Clinic on Psychosomatic Problems

A Case of Persistent Ankle Pain in Spite of Adequate Orthopedic Treatment

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric Services of the Massachusetts General Hospital. This psychiatric conference was edited by Dr. Stanley Cobb.

DR. FREDERICK WHISKIN: The patient's present illness began in August, 1947, when she was thirty-six years of age. She was involved in a bus accident in which she suffered an injury to her left ankle. Since that time two fusion operations have been performed, she has had a sympathectomy and a sympathetic block with no relief of her symptoms. She sued the bus company and finally settled out of court. In July, 1953, the patient was seen in the orthopedic clinic of this hospital where an x-ray was taken which showed "solid fusion with disuse osteoporosis." She was seen again in October, 1953, and admitted to the Orthopedic Service. Their opinion was that she had more pain than would usually be present with the degree of orthopedic abnormality present. She was transferred to the Psychiatric Service October 28, 1953, and has now had four months of a combined therapeutic approach, with the cooperation of the Orthopedic Service, Physical Medicine Department, Social Service and Occupational Therapy. She has shown considerable improvement. She is able to take a few steps without crutches now and is thinking more realistically about her future problems.

Personal History: She believes that she had a "normal childhood" except for marked feelings of inferiority about being obese and sex play about which she feels very guilty. The home atmosphere was strict and moralistic, with much religious talk. She was interested in music as a child and studied it throughout her school years, majoring in music for two years after completing high school. She worked with her father for many years as pianist and organist. They traveled around to many cities, and she describes having numerous sexual experiences. She was greatly disillusioned by all this and felt hurt that the very people whom she had placed on a pedestal would behave in this manner. In 1945 she worked as a bookkeeper and later started doing medical assistant work. In 1946 she had changed to working as an assistant in a physician's office. It was during her second year at this work that she sustained her injury.

The patient's medical history reveals that she had had an appendectomy performed in 1930, also a right-sided mastoidectomy. In 1934 she was in the hospital with an "intestinal hernia"—it is not known if she had an operation or not at that time. In 1940 she had a cholecystectomy. In 1941 she had a "relapse"; she had some urinary symptoms and a cystoscopy was done. In 1943 the patient had "trouble with kidney stones"; she was seen by a doctor who "watched it until it passed." In 1944 she developed gynecologic symptoms and was admitted to a New York hospital where it was discovered that she had endometriosis. They did a "retroversion of the uterus" at that time. In May, 1947, the patient submitted to hysterectomy.

It was in August of that year that she had the bus accident. Her left side was hurt. Her head smashed into the windshield but she was not unconscious. She picked herself up and found that she could not step on her left foot. She was taken to an orthopedic surgeon who put her ankle in a cast and sent her home. She tried to work but could not. The only time that she was without pain during this period was when her foot was immobilized. She was told that she had two choices—braces for the rest of her life, or surgery. She chose to have surgery. Also she began court action and after two years a settlement was made. Fusion of the left ankle was performed in 1948 but was not successful. This was repeated in June of the following year. In

November, 1949, the patient had a sympathectomy. She did not respond well and was sent to a sanitarium for ten months where psychotherapy was given once a week. She then tried to go to a laboratory school but "cracked up" and was sent to a mental hospital. There she had six "shock treatments," then sustained a rib fracture so that she could have no more. Also a disturbed patient fell on her and reinjured her ankle. She returned home and stayed there most of the time after this until the present admission.

The patient's family history reveals that her father and mother are living and well. She describes her mother as being a very nervous person. She has three brothers and a sister. She describes her parents as being very strict and extremely religious. She was never allowed to smoke at home, this being considered a major sin. She feels that her mother was jealous of the relationship which she had with her father, and apparently was upset by her mother's "nervous spells." Her father and mother are people who rarely show their feelings and became very uneasy when the patient would show hers.

Physical examination on admission showed an obese white female with normal findings except as follows: (1) left ankle fusion, (2) cold cyanotic left leg and foot to knee, (3) intense pain felt across ankle on moving subastragaloid, mid-tarsal and metatarsal-phalangeal joints and (4) left lumbar sympathectomy scar. Laboratory findings were not remarkable. An x-ray taken October 13, 1953, showed fusion of the left ankle with no changes in the mineralization of the bones since the last examination. The orthopedic diagnosis was fusion of left ankle, with persistent pain and Sudeck's atrophy.

A psychiatric consultant advised admission to the Psychiatric Ward for evaluation and therapy. On admission to the Psychiatric Ward, she was described as an obese white female looking much younger than her stated age. She walked on crutches but gave no sign of being in severe pain. Her stream of talk showed no blockage and its content was logical and coherent. Her mood was slightly depressed. She spoke in a low tone and appeared inhibited and self-conscious. She was well oriented as to time, place and person; showed no delusions, illusions or hallucinations. She voiced considerable hostility because she believed that psychiatrists had made her worse by "forcing her to talk about unpleasant things from her past." She seemed of average intelligence and had some degree of insight.

My impression at that time was that the patient had a difficult and complex problem, a combination of tissue injury and a severe hysterical character disorder with depressive trends. She probably had been neurotic long before her injury but was able to carry on in a borderline adjustment. The injury was enough to disturb this adjustment and cause her to regress to an infantile, dependent level. All this was intermingled inextricably with her symptoms of pain. It was decided that an attempt should be made to keep the interviews limited to the reality situation and that a probing kind of therapy should be avoided as much as possible. A combined approach was arranged with the cooperation of the orthopedic service, physical therapy, occupational therapy and social service. The patient was under considerable sedation and codeine when she arrived on the Psychiatric Ward and this was to be removed gradually.

During her four-month stay on the Psychiatric Ward the patient has shown slow but definite improvement. Although she still complains of many fears, she now is ready to contemplate returning home and from there to work at a part time job. She is now not receiving any sedation at all. She walks with crutches but is able on occasion to walk a few steps without them. The Orthopedic Service has made a special boot for her which gives her a good deal of weight support and eases the pain considerably. Endocrinological consultants believe that she almost certainly had an artificial menopause. They did not believe that she had menopausal osteoporosis but did recommend estrogen therapy for the menopausal symptoms.

About a month and a half ago the patient became particularly tense and anxious and was given small doses of insulin, 20 units daily in the morning, which seemed to ease her anxiety a good deal. She complained also of a heavy feeling of depression on occasions and small doses of dexedrine were prescribed which apparently helped her a good deal.

First Staff Conference—March 4, 1954. A brief history was presented by Dr. Whiskin. The patient came in for an interview by Dr. Cobb. She walks into the room without crutches. She says that she had some relief of pain after the nerve block but that there is still some deep pain in the joint. She knows that the pain makes her irritable and that emotional stress makes the pain worse. She hopes to get to work gradually but gets no cooperation at home. She feels she must

get free. She realizes more than ever that she has a lot of fears she has had to face.

DR. COBB: She has had about eighteen weeks on our ward with a combined type of therapeutic approach. What did the psychologic examinations show?

DR. ROSENBLUM: I examined the patient last week. She was quite apprehensive about taking the tests. She immediately said that she had a headache but made no more mention of it until the last Rorschach card when the stress became too much for her. She again complained of her headache which was now "terrible" and testing was terminated, but she was given blanks to fill out over the weekend. The most impressive thing in the Rorschach test is the intense preoccupation and concentration on anatomic responses. Of twenty main and additional responses, ten were concerned with portions of the anatomy, largely the spinal area, the lungs and the kidneys. Although some of these percepts were well articulated on the blots and were even considered original, just as many others were vague, poorly articulated, and not at all related to reality. This type of response is usually indicative of a serious mental disturbance. Many hypochondriacal and psychosomatic patients develop a plethora of anatomy responses. In this patient her concern about her hostile impulses are fraught with anxiety and tension. She appears to be rigid and anxious in her interpersonal relations. This marked fear of people pervades her sentence completion test. She is a self-conscious, insecure, depressed person overwhelmed by life. The nature of her disturbance appears to be severe and deep rooted. She has average intelligence.

DR. COBB: One therapist tried hypnosis on her, I believe. How traumatic was it?

DR. WHISKIN: It was traumatic, because it was the wrong type of treatment for her. She made use of the feeling of having been forced to keep up her symptoms.

DR. COBB: What does she talk about in the interviews?

DR. WHISKIN: Masturbation, sexual experiences, attractions to young boys.

DR. COBB: Other psychotherapists have gone into sex misconduct as if it were the main point and made her feel more guilty about it. The feelings of lack of support and disillusionment are more important. How about her mother?

DR. WHISKIN: She had dependence but hostility; her mother was nervous and tried to control the patient by getting intense and upset. The patient becomes angry with her.

DR. COBB: Do we have any social service report?

MR. WYSOCKI: I have been trying to work on a realistic level. She speaks of her father only as a kind, warm man. She talks of her mother as the cause of the trouble. This was very vague. I tried to work backward. She spoke of being a bookkeeper, and of working for doctors. She expressed feelings of hostility toward the hospital personnel. It is hard to get her to stick to talking about making plans. She thinks she will not be able to work because of a symptom that has progressed from her ankle to other parts of her body.

DR. COBB: She probably has a vague line between fact and fantasy. How does she impress the nursing staff?

MISS NEEDHAM: She is demanding and complaining. She had pains everywhere and always wanted medicine. She was not satisfied with what we gave her; moody; did not socialize much.

DR. SHARPE: How was it possible to get her to discontinue sedatives?

DR. WHISKIN: We reduced them gradually and there was a good deal of hostility connected with it. Headaches are her main complaint now, a feeling of pressure in her head which makes it difficult for her to think.*

DR. COBB: We ought to begin with some idea of the cause of the pain mechanically; there was certainly a bad sprain or perhaps fracture. I suppose there was marked mechanical pain in the beginning and that this has persisted with a large psychologic element. She has good fixation by the fusion operation so the psychologic factor is the only one we can be helpful on.

DR. NEMIAH: There are some curious discrepancies. Listening to the history, one recognizes the type of patient we see in our cases with low back pain. It is the old problem of chronic illness and rehabilitation. She has poor relationships, is demanding and hypochondriacal. Why is there this feeling about not probing, and treating her in a supportive way? If you do that you will not discover what the symptoms mean. This is the type of patient who uses denial as an important mechanism. They say immediately that they have no psychologic problems. Find out what the anxiety means and lead to the

* The patient is brought in and interviewed by Dr. Cobb.

symptoms. This is not the sort of person one must be too careful with. She talks about being anxious and afraid.

DR. WHITE: I did not want to go much further into this because I think we have some idea what she is anxious about. She is using pain to cover up what is inside of her, namely, her destructive impulses and aggressive wishes toward men.

DR. NEMIAH: I am not talking about sexual fantasies and aggression. What she presents is "I am scared about going to work." It seems to me that one could work gently and carefully in that area. What defenses does she have?

DR. WHISKIN: She has spoken of feelings of hostility quite readily. She says she has them but is unable to express them and is afraid of them. Although you are right that we could learn more by probing more, we might stir up a schizophrenic reaction.

DR. COBB: From the Rorschach test we have reason to believe that she has severe hypochondriasis. That is one step from a schizophrenic reaction.

DR. WHISKIN: She will talk about her fears. She is afraid of dealing with reality. Whatever I said she worked into a criticism. I tried to indicate that this was a projection of her own hostility.

DR. COBB: She distorts things in such a way that everything is something somebody did to her. It is always the other fellow's fault. She puts you into that situation.

DR. WHISKIN: I think the mechanism of pain is chiefly masochistic.

DR. COBB: The word "masochism" means having sexual outlet through pain. But the term is often used broadly to mean anything people do to make themselves suffer, whether related to sex or not. It looks as if she was enjoying pain, using it and holding on to it. How much sexual meaning that has in her case I do not know. Obviously, continuation of the pain stops her from holding a job, meeting people and being exposed to the fears she talks about.

DR. CARTER: I think the pain serves another function, giving her a channel for hostility which is permissible. She can say that the doctors have mishandled this. In speaking about doctors, there is an undertone of hostility.

MR. WYSOCKI: A couple of weeks ago a deadline was set for discharge. I saw her then and she spent two interviews expressing her anger and hostility about being unprepared to go out in the community.

DR. WILLIAMS: I would like to know what her work record is. I have the impression that she is fearful of getting into a job, of taking a step.

DR. COBB: Taking a step is exactly what she is afraid to do. I think the experiment of sending her home is excellent but we will probably have her back. You can point out that she is holding onto the pain, but never say that the pain is not real. What she probably has is an exaggeration of slight pain, which thus becomes disabling. Patients accept that explanation more easily.

Short trials of living at home were unsuccessful. The patient stayed on the ward most of the time for the next four months. She was seen in psychotherapy three times a week. The interviews were directed toward reality adjustment but it was difficult to get her to think along the lines of what her future adjustment was to be, what type of job she would have, where she would live, etc. Rather, she seemed intent on getting some kind of masochistic gratification from the interview. She was extremely self-conscious, blushed a lot and complained a great deal. This type of activity on her part was consistently pointed out to the patient. After about ten weeks the patient began to realize how her neurosis has tended to distort the reality of the doctor-patient relationship. She stated that she had thought of the doctor as a stern, frightening, critical person like her father, but now she was able to see him as a reasonably objective person who wanted to help her. During the last ten or so interviews the patient has begun to speak of fear in relationship to sexual feelings. A great deal of guilt and conflict over masturbation was ventilated. She relates her ankle pain and difficulty in walking to a fear of "what she would do if she could walk"; if she could walk she would either "run away" or "get involved," the latter meaning having an affair with a man, usually an older man. She states that when she masturbates she has strong feelings of hate which frighten her. The problem of being afraid of strong hostile feelings which she must constantly keep in control is a constant theme running through each interview. She has depressive feelings which she relates to the high standards which she can never live up to. She describes herself as a perfectionist. During the therapy she has found herself more relaxed and able to do things without constantly thinking, "what are others thinking of me?" The patient is given considerable support through all this, her positive assets being pointed

out to her whenever she gives the therapist a chance.

As she began to improve she was given a strong suggestion by Dr. Whiskin that she must walk without crutches, at first in her own room and finally out on the ward. Nurses aided in this effort and she began to walk more and more.

A novocaine nerve block was tried in June, 1954.

About four months after the first staff meeting and eight months after her transfer to the Psychiatric Service, she was brought up for a second staff meeting on June 29, 1954.

Second Staff Conference—June 29, 1954. The patient walks into the room without crutches.

Miss Sherwood: The patient wanted to go home and now feels that did not work. She wants to know where to go from here. She is now seeing a person from vocational rehabilitation to get a job, but she wants to go gradually. She wants to live in Boston but has no resources for doing this. The Welfare Department believes she can get a part time job.

Dr. Ludwig: These patients are very difficult to deal with. One finds them on orthopedic and neurosurgical services. In this instance the neurosis was present long before the operations. I had one case concerning which the orthopedic surgeon said: "These people almost make you operate on them." They are like addicts. They have a masochistic need to be mutilated. As soon as we let up or there is a loss of support, they go back for more operations.

Dr. Cobb: She had made a precarious adjustment to her father, brother and mother; but she had made it. Then she gets an automobile accident and a chance to sue. She gets thrown into a round of pain, lawyers and arguments. That is the ideal situation to precipitate the whole neurosis. "Polysurgery" is not a diagnosis; it is a result of the situation.

Dr. Nemiah: This has a very familiar ring. Three things are striking: First, she is now able to give better expression of her feelings. Second, here is a woman who got a settlement, yet she did not improve. She may have lost an important defense against narcissistic dependency. The third important thing is: she is ripe to get back to work. If we miss this opportunity she will relapse.

Dr. Lindemann: A good start has been made. I am sure we are not through with her. She will seek us out again. She thinks she ought to have a lot more treatment. The immediate problem is how to transfer her to another doctor without having her slip back when Dr. Whiskin leaves. Whoever takes her should see her in the presence of Dr. Whiskin.

She is up against a social situation which she is not able to handle alone. She was once apparently able to handle it, and there must have been certain circumstances that made it possible for her to hold a job. Knowing how she did that might make it possible for her to do it again. One problem is that a lot of the help to rehabilitate her has come from people who have to acknowledge that she has some "real" difficulty. She has something she calls "real" and something she calls "psychologic." We have the problem of getting rid of the conversion aspect, but we have to help her to live with the defect. Those are two different operations. I think her tendency to distinguish the two is a valuable one. If she can abandon the conversion aspects and see to what extent she is reasonably comfortable with the defect, there is hope for real progress.

She can lean on the pride of achievement. Abandoning a conversion symptom is humiliating. Mastering a defect is considered very important. We must put the emphasis on the side of achievement. This may come from the social service more than from the psychiatrist. Perhaps the psychiatrist, rather than trying to continue to deal with the aspects of sexuality, should first get her established as a going concern in a remunerative situation. When she feels she is a real person who achieves something, one might then take up the problem of sexuality. She could then face the question as to whether she is a person who may properly love someone and properly have a family. In any case she will remain a problem of skillful handling.

Dr. Whiskin: She is going to stay with Mrs. Duke. If she gets into trouble, she can come back on the ward. Otherwise there will be no one to see her.

Dr. Lindemann: Then she has to use new symptoms as an admission ticket to get back.

Miss Sherwood: She is very busy working on things to get out of her parents' home, the first positive step to do something on her own. While I am away another social worker is arranging for her to come in once a week to discuss her plans.

Dr. Cobb: If she has the momentum, let's have her try. If she fails, I would not accent it too much. I said to her, "we will look after you."

That might support her without telling her that she will need a symptom to get back into the hospital. It is an interesting job.

It is important that practicing physicians realize that psychiatry is able to help in these surgical situations that are not usually considered psychiatric. Chronic pain following injury and continuing after adequate orthopedic treatment is a great problem to the insurance companies. If we as physicians can learn how to recognize and treat such cases with definite psychologic factors, we can be of great help to our medical and surgical colleagues. We must move cautiously and get more experience before we make pronouncements, because this is a new field for psychiatry. But if we can help more patients as we have helped this one, and the one recently reported by Dr. Nemiah,* we can begin to have a feeling of achievement.

Continued Follow-up. The patient has moved away from her difficult home life and is now living in a room and working as a typist. She is adjusting fairly well but is in an acute anxiety state about leaving home and hospital. Her feelings toward her mother are more acute as are her feelings about being let down by her doctor, who left. This causes feelings of inadequacy and helplessness. She is now being seen twice a week in the Outpatient Department by a doctor and once a week by the social worker.

* NEMIAH, J. C. A case of low back pain complicated by psychologic factors. *Am. J. Med.*, 15: 391, 1953.

Clinico-pathologic Conference

Extreme Physical Effort in Summer Heat Followed by Collapse, Stupor, Purpura, Jaundice and Azotemia

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. A. (No. 239055), a twenty-nine year old white male social worker and amateur long-distance runner, was admitted to Barnes Hospital for the first time on the evening of June 18, 1954; one hour previously he had collapsed soon after completing a 6 mile foot race.

The patient, a resident of New York City, had been in good health all his life. On the day of admission, which was very hot and humid, he felt tired and very thirsty and took three dextro-amphetamine tablets, which he had never done before, in preparation for a race. About one hour prior to admission the patient had finished fourth in a 6 mile national A.A.U. foot race; immediately thereafter friends walked him around for about ten minutes; he then collapsed. At the field he was observed to be cyanotic, intermittently pulseless and having Cheyne-Stokes respiration. He vomited food once on the field. When palpable his pulse rate was 130 and regular. Following a period of unconsciousness he had a period of aggressive and maniacal behavior associated with frothing at the mouth and extreme sweating. He was brought to Barnes Hospital confused, hot, sweating, aggressive and suspicious.

The patient had engaged in amateur long-distance running contests for many years. While working as a social worker in New York he had visited in recent weeks a number of homes in which jaundice had occurred or was present in some member of the family. He had also been exposed to a fluid used in the cleaning of a duplicator machine which was used for printing a newspaper. The patient drank alcoholic beverages only rarely. The past history and family history were non-contributory.

Physical examination at the time of admission revealed the patient's temperature to be 39.2°C., pulse 120, respirations 15 and blood pressure 80/40. The patient appeared to be a well developed and well nourished young man who was pale, hot, sweating and confused as to time and place. He had amnesia for the events immediately prior to admission. He was not cyanotic. Examination of the eyes revealed the pupils to be small but they reacted to light. Extraocular movements were normal. Ocular fundi were not remarkable. Examination of the neck revealed no stiffness or thyroid enlargement. The lung fields were clear; the heart was not enlarged, there were no murmurs and the rhythm was normal sinus. Examination of the abdomen revealed slight rigidity with normal bowel sounds. No masses were palpable. The admission physical examination made no mention of hepatomegaly but on subsequent examinations the liver was enlarged to 4 cm. below the costal margin and tender. The remainder of the physical examination was not remarkable.

The laboratory data were as follows: hemoglobin, 18.9 gm. per cent; white blood cells, 9,250 per cu. mm.; differential blood count: stab forms, 14 per cent; segmented forms, 69 per cent; lymphocytes, 6 per cent; monocytes, 11 per cent. The red blood cells and platelets appeared normal. Urinalysis: specific gravity, 1.018; pH, 4.5; protein, 4+; sugar, negative; centrifuged sediment, 2 to 4 coarse granular casts and a few pus cells per high power field. Stool examination: guaiac-positive. Blood cardiolipin reaction:

negative. Blood chemistry: non-protein nitrogen, 46 mg. per cent; sodium, 150 mEq./L.; potassium, 4.6 mEq./L.; carbon dioxide combining power, 17.3 mM/L.; chloride, 119 mEq./L.

Immediately upon admission the patient was given intravenous fluids, receiving 3 L. by the following morning. He was also given a cool sponge bath with ice bags placed at both axillas. He occasionally vomited small amounts of pink fluid, and expelled a large amount of diarrheal stool. His blood pressure and pulse rapidly returned to normal levels, and on the morning of the second hospital day, approximately twelve hours after admission, he was alert, cooperative and apologetic. His temperature was 38.3°C. Until the third hospital day he continued to vomit intermittently and to run a low grade fever. On the fourth hospital day his emesis was noted to resemble "coffee grounds" in appearance and to be guaiac-positive; the pH was 5. A roentgenogram of the chest on the fourth hospital day was interpreted as negative.

Because of abdominal pain and persistent vomiting, the patient was placed on Wangensteen gastric suction; his fluid balance was maintained by intravenous fluids, and he was given 2 units of blood. Blood chemical determinations on the fourth hospital day were as follows: non-protein nitrogen, 32 mg. per cent; fasting blood sugar, 6 mg. per cent; sodium, 142.3 mEq./L.; potassium, 3.0 mEq./L.; carbon dioxide combining power, 12.5 mM/L.; chlorides, 106 mEq./L.; amylase, 160 Somogyi units. At 7:00 P.M. on this same day the blood sugar was found to be 12 mg. per cent; no convulsions or irrational behavior were observed at that time. On the fifth hospital day it was noted for the first time that the patient was icteric, and that he exhibited bilateral conjunctival hemorrhages. An electrocardiogram obtained that day was reported as within normal limits. On the morning of the fifth hospital day the patient pulled out the intragastric tube, a succussion splash in the abdomen was elicited and the abdomen became tympanitic. On the fifth hospital day the following examinations were performed: bleeding time (Duke), 20 minutes; coagulation time (Lee-White), 27 minutes. Blood chemical determinations were as follows: non-protein nitrogen, 56 mg. per cent; sugar, 78 mg. per cent; sodium, 131.1 mEq./L.; potassium, 4.9 mEq./L.; chloride, 103 mEq./L.; carbon dioxide combining power, 17.5 mM./L.; prothrombin time, less than 10 per cent of normal; cephalin cholesterol flocculation, 3+; thymol turbidity, 0.7 units; total bilirubin, 12.8 mg. per cent; one minute fraction, 5.6 mg. per cent; protein, 5.2 gm. per cent; albumin, 4.1 gm. per cent; globulin, 1.1 gm. per cent; alkaline phosphatase, 4.9 Bodansky units. A complete blood count was as follows: red blood cells, 4,210,000; hemoglobin, 13.5 gm. per cent; white blood cells, 13,550; differential: juvenile forms, 1; stab forms, 17; segmented forms, 77; lymphocytes, 2; monocytes, 2; platelet count, 160,000 per cu. mm. An iliac crest bone marrow was described as follows: "cellular marrow; myeloid and erythroid cells appear normal. There is a slight depression of erythroid cells on the differential count. Megakaryocytes appear normal. There is a slight increase of fat and hemosiderin. Marrow is not diagnostic." Another bleeding time (Ivy) was greater than 12 minutes, and a coagulation time (silicone tube method), 85 minutes. The patient was started on intravenous tetracycline, receiving 1 gm. each day. On the sixth hospital day an indwelling urinary bladder catheter was inserted. The prothrombin concentration was 21 per cent of normal, and the blood hematocrit was 40 per cent.

On the fourth hospital day the patient was much more restless and was occasionally irrational, for which he received intramuscular injections of sodium phenobarbital in amounts of 0.05 to 0.12 gm. Monosodium glutamate was added to his intravenous fluids beginning on the seventh hospital day. On the eighth hospital day he lapsed into coma, interspersed with periods of maniacal behavior. The jaundice increased, there were massive orbital hemorrhages and the neck became stiff. The patient's urine output after the fourth hospital day never exceeded 645 cc. However, his emesis varied from 1,000 to 2,600 cc. His blood pressure began rising on the seventh hospital day and gradually rose to a peak of 180/122 on the ninth hospital day. Blood chemical determinations on the ninth hospital day were as follows: sodium, 144 mEq./L.; potassium, 4.9 mEq./L.; cholesterol, 130 mg. per cent; fasting sugar, 113 mg. per cent; non-protein nitrogen, 204 mg. per cent; carbon dioxide combining power, 18.9 mM/L.; chloride, 110 mEq./L.; prothrombin concentration, 19 per cent of normal. He was started on 100 mg. of cortisone every six hours, 0.5 gm. of streptomycin every eight hours and 600,000 units of penicillin every four hours, all given

intramuscularly. On the morning of the tenth hospital day the patient had two convulsions with chewing of the tongue and jerking of his right arm, following which he had stertorous breathing. He was given 10 ml. of calcium gluconate (10 per cent) intravenously. At that time his blood pressure was 112/60, his temperature 40°C. About one hour later the patient had a third convulsion, following which his respirations stopped. His pulse and blood pressure were unobtainable. Immediately prior to the last convulsion the temperature was found to be 41°C., and a tepid water sponge bath was begun along with the intravenous administration of 1,000 cc. of 5 per cent glucose in normal saline which contained 1 gm. of sodium salicylate. He died June 27, 1954.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: Dr. Milton Smith, who took care of this patient, tells me that this man was associated with the Pioneer Athletic Club in New York. This club held qualifying races and field events in order to select members best able to represent this club at the National Amateur Athletic Union's track meet in St. Louis on June 18, 1954. The patient we are considering did participate in these qualifying track events, and failed to qualify in the 6 mile race. This is important in that the club did not send him to St. Louis at their expense. He had very limited financial resources, but was very anxious to run, so he hitchhiked to St. Louis. This may be of considerable importance. We do not know how long it took him to get here but the weather was very hot and it is safe to assume that he arrived tired, dirty and hot. It is perhaps of interest that this patient several years previously had run in the Boston Marathon, a distance of 26 miles, when the temperature was about 90°F., so that he had been exposed to hot weather racing before without getting into trouble. The patient apparently told somewhat conflicting accounts to different questioners concerning the state of his health when he responded to the starter's gun of this 6 mile race. He told one observer that he had not felt quite up to par for several days. The significance of this is certainly questionable, in view of the fact that these several days were spent in hitchhiking to St. Louis. The only specific information we have regarding his health during the days immediately preceding the race was the statement by the patient's wife to the effect that one month prior to the race he went to a physician because of pain in his right side. We know nothing more about this, but the doctor said he was all right, gave him no treatment and he had no further trouble from this symptom. Now, while in the hospital here he had chest x-rays taken, which were interpreted as showing no significant disease or abnormalities so far as the lung fields and the heart are concerned. Dr. Shank, I would like to begin by focusing our attention on this patient's jaundice. Unless you disagree, let us assume that this was intrahepatic jaundice; would you discuss the various etiologic agents of liver disease that might have been present in this patient, with particular reference to the history of casual contact with several jaundiced individuals and their families, and further, the possible significance of the exposure to a fluid used in cleaning a duplicating machine.

DR. ROBERT E. SHANK: I believe when I first saw this patient, on the fourth day of his illness, that he had hepatic degeneration. The problem then was to review this history and to attempt to get more information. It may not be clear from the protocol that the patient, himself, was not capable in those first few days of totally satisfactory response to questioning. On the day that I first saw him his wife had arrived from New York and could provide additional help. This man worked as a social investigator in the area of the Presbyterian Hospital in New York. He was training to be a social worker but had not yet gotten this degree. In this capacity he visited in many homes in the Harlem area of New York, where he was in contact not only with many young patients who had jaundice, but also worked in a neighborhood in which there were rats. He did not at any time have a rat bite. Another factor in the history that seemed of some importance for us to pursue further was the fact that the patient and his wife were responsible for producing a little newspaper called "Track and Field News," which is apparently the journal for this particular amateur athletic group. His wife reported to us that they had rushed to get out an issue of this newspaper during the week preceding the A.A.U. meet in St. Louis. The patient, in what seemed to be a lucid interval, corrected that statement, however, and said that it had been several weeks since they had used the machine with which they had produced this newspaper; in cleaning this machine they used a fluid, the

name of which he did not know, but he thought that one part of the name was "carbon," presumably carbon tetrachloride. Unfortunately, we could not establish exactly the last time he used this material. So much for the history. At the time that I first saw this patient he had a palpable, tender liver extending down about 4 cm. below the right costal margin: he was icteric, had purpuric manifestations throughout his skin and also massive hemorrhages into the conjunctivas. Gastric suction was being used at the time and a "coffee grounds" material was being suctioned back. To me at this time, the entire picture represented acute hepatic necrosis due to an unknown cause. It certainly seemed possible that at the time he made his trip to St. Louis to participate in the race he might have been in the early stages of viral hepatitis. Both he and his wife described the right upper abdominal discomfort which had bothered him for a period of a month, for which he saw a physician who could find nothing abnormal. Thereafter he had disregarded the discomfort, but it had nevertheless persisted. Furthermore, we were interested in his complaints on the day of the race. He came to St. Louis by a combination of hitchhiking and bus travel, arriving here about midnight the night before, and had thus managed to get some sleep. He not only was tired the next morning but he was also very thirsty, and stated that he drank rather large quantities of fluid on the day of the race. Furthermore, because of this complaint he consulted his coach and other members of his athletic team who advised him to take what he said was dexedrine,® a total dosage of three tablets prior to the race. These complaints force us to consider the possibility, at least, that he may have been developing early hepatitis just at the time when he participated in an event in which there was excessive physical activity and also a hot climate. Whether this might have been a toxic hepatitis resulting from exposure to carbon tetrachloride was, we thought, less likely, although the presence of renal damage as well as of hepatic damage could have been compatible with either fulminant hepatitis on a viral basis or with toxic hepatitis. At the time I saw the patient, we were uncertain of the possible origin and that uncertainty probably still exists.

DR. REINHARD: Some thought was given to the possibility of Weil's disease, a disease characterized by fever, nausea, diarrhea, hepatitis and nephritis, all of which the patient showed. I am sure there are rats in Harlem. Does this need to be considered?

DR. SHANK: We considered it at the time that we were working this patient up. Although he had hemorrhages in the conjunctivas, the man did not complain of muscular pain, there were none of the cardiac abnormalities or electrocardiographic changes that are sometimes associated with Weil's disease, and there was no history of rat bite. All that we had was a vague history of being in an area in which there were rats. I think at the time I leaned more strongly to a diagnosis of early viral hepatitis with the further insult of heat and excessive activity.

DR. REINHARD: Certainly the absence of muscular pain, headache and photophobia are against Weil's disease. Now, Dr. Mendeloff, how about Chiari's syndrome? This was also considered clinically. Do you think this needs to be given serious consideration?

DR. ALBERT I. MENDELOFF: Chiari's syndrome would be unlikely to appear so rapidly without more evidence of acute portal hypertension. That syndrome is generally more chronic; the liver usually is not only very large but also very firm. If this patient had been as ill as this with Chiari's syndrome I would have expected to find splenomegaly and ascites to go with it.

DR. REINHARD: He had neither of those findings. The only other data I want to add to the protocol has to do with the weather on the day of the race. I called Mr. Wahlgren at the St. Louis Weather Bureau, explained why we were interested in this, and received a long letter from him together with a very impressive array of charts. These charts contained half-hourly temperatures, relative humidities, wind velocity, etc. In St. Louis on June 18th at 4:00 P.M. in the afternoon the temperature was 96°F., the relative humidity was 39 per cent. This race was run in the evening at approximately 8:00 P.M., at which time the official temperature was 86°F. Relative humidity had gone up to 54 per cent. The wind velocity in the afternoon averaged 7 miles per hour. In the evening there was a slightly stronger breeze blowing. The average temperature for this particular day was 10 degrees above the normal for June 18th, so this was a hot, humid day. The patient came from New York City which was enjoying rather balmy weather. The maximum average daily temperature in New York City for the week preceding the time this man came to St. Louis

was 77°F. The average minimum daily temperature there was 61°F.

We should certainly say a few words about the types of heat disability which might pertain to this patient. The manifestations of heat disability have been classified into three categories by Malamud et al. in an excellent article.[1] The first is heat cramps, which I think we need not consider as being pertinent to this case. The second category is that of heat exhaustion, which covers a wide range of symptoms. The temperature may be normal or subnormal but is usually slightly raised, and may reach 101°F. Ladell, Waterlow and Hudson[2] summarized their experience with heat exhaustion, stating that there were two types of this disorder; one a syndrome due to salt loss in the patient, occurring during the hottest weeks in the summer, manifested chiefly by giddiness, anorexia, headache, cramps, vomiting, sweating and evidences of dehydration, and secondly, a syndrome which they called "breakdown of defense mechanism against heat," essentially a derangement of the mechanism of sweating. This occurred in the latter half of the summer and was characterized by dizziness, exhaustion, anorexia, insomnia, dyspnea, abnormalities of sweating and often polyuria. The third broad class of disability due to heat is heat stroke, sometimes referred to as heat hyperpyrexia. This usually comes on suddenly and dramatically, although it may come on more gradually with premonitory symptoms; it is distinguished by failure of the sweating mechanism, by delirium with coma, convulsive seizures, circulatory collapse and the like. In heat stroke the temperature is usually markedly elevated, over 106°F. in the majority of the cases. Sunstroke belongs in this group and at one time it was believed that the direct effect of the sun beating on the head had a bad effect on the nervous system. It is generally accepted now that the effect of the sun is simply its role in increasing the heat load. In determining whether a given patient has developed heat stroke or not, the obvious environmental conditions—the temperature, the humidity and wind movement—are very important. The age of the patient, his general physical condition and the degree of muscular exercise are equally important. One should emphasize that the heat loss from the surface of the body must be maintained in order to keep the body temperature normal; this loss is about five times greater when a person is running rapidly than it is at rest. Unsuitable clothing will aggravate the possibility of heat stroke occurring. I want to emphasize also lack of acclimatization as an important factor. Dr. Klingberg has been very much interested in these problems in connection with his work as a reserve officer in the Army Medical Corps, and has studied them very carefully. He was asked to see this patient on those grounds. He was the first to suggest that all this patient's clinical manifestations might be attributable to heat stroke. Dr. Klingberg, would you discuss the factor of acclimatization in these cases?

DR. WILLIAM G. KLINGBERG: It is probably one of the major factors, at least in the army groups that hold maneuvers in the extremes of heat, particularly in the desert, where humidity is low. It takes at least a five-day period to acclimatize a person adequately to the effects of intense heat. This particular man came from an area where the temperature was low, directly into an extremely hot temperature and certainly had not had time to acclimatize himself. We can add to the high temperature the high humidity and the resultant inability to depress body temperature by sweating in an efficient manner.

DR. REINHARD: Dr. Schroeder, this patient developed symptoms immediately after the race. He was admitted to Barnes Hospital approximately one hour later. He died nine days later. Do you think this sequence of events is compatible with heat stroke? It has been emphasized in the literature that if the patient survives the first twenty-four hours, complete recovery usually occurs. Do you think this is correct?

DR. HENRY SCHROEDER: He must have had something else besides heat stroke, but shock, exercise, heat and a number of other stresses are not very good for livers that are partly damaged, as we know. It is probable that the underlying process in the liver was accentuated markedly by this great heat disability from which he suffered.

DR. REINHARD: It is well to emphasize here that patients who have no disease except heat stroke may have a more prolonged duration of symptoms than twenty-four to forty-eight hours. In the series of ninety fatal cases of heat stroke reported by Malamud in which there was a reliable history, 70 per cent died in less than

[1] MALAMUD, N., HAYMAKER, W. and CUSTER, R. P. Heat stroke: clinico-pathologic study of 125 fatal cases. *Mil. Surgeon*, 99: 397, 1946.

[2] LADELL, W., WATERLOW, J. and HUDSON, M. Desert climate—physiological and clinical observations. *Lancet*, 2: 491, 527, 1944.

twenty-four hours; thirteen patients died within twenty-four to forty-eight hours, but seventeen of them lived from forty-eight hours to as long as twelve days, so that the prolonged duration of symptoms certainly does not exclude the possibility that our patient might have been suffering only from heat stroke. This patient came in with a temperature a little above 40°C., which dropped to lower levels very promptly. He then ran an irregularly febrile course in the hospital; the temperature reached what we would consider truly hyperpyrexic levels only terminally. Most of the reports in the literature emphasize that in heat stroke hyperpyrexia usually approaches 106°F. It disturbs me somewhat that this patient never had a temperature in this range from the time he was admitted to the hospital until the time he was in a terminal phase of his illness. Dr. Shank, does this bother you?

DR. SHANK: Yes, it does; I would like to ask further whether we really can call this heat stroke. This man was sweating profusely when he came in with his elevated temperature. I would like further discussion on the use of that term here.

DR. KLINGBERG: The majority of individuals with heat stroke will have failure of sweating and hot dry skin. There were three patients of 125 reported in the Malamud paper who had excessive sweating. It is certainly well recognized that individuals can begin with heat exhaustion and then have heat stroke develop. With heat exhaustion excessive sweating is a characteristic symptom; this patient undoubtedly sweated profusely, and we know that on the day of the race he drank large quantities of fluid, probably water without added salt. The replacement of the fluid lost by water without salt might become important as a method by which heat exhaustion may be converted into heat stroke.

DR. REINHARD: Dr. Schroeder, this patient's blood pressure in the emergency room was 80/40. Within a period of about an hour his blood pressure had risen to 120/70; on the third hospital day his blood pressure was about 130/40, but at no other time during his stay in the hospital did he have a really severe hypotensive blood pressure level. Would you believe that this would rule out the possibility that this patient had heat stroke?

DR. SCHROEDER: I am not sure just where the dividing line is between heat exhaustion, which can certainly lead to a lower blood pressure from loss of blood volume and loss of body fluids, and this irreversible syndrome of heat stroke, characterized by absence of sweating. This patient was probably in that earlier phase, and recovered from shock rapidly by simple replacement of fluid and salt. In this later episode he was probably manifesting renal damage.

DR. REINHARD: I personally hesitate to attribute all these clinical manifestations to heat stroke because this patient did not have a more profound, and particularly a more prolonged, severe hypotension. In the hepatic necrosis occasionally seen in heat stroke there are two factors that may contribute. One is the hyperpyrexia which directly affects the liver cells, and the other is the shock which can affect the liver cells as well as the central nervous system, for example.

DR. KLINGBERG: He certainly had shock probably for as long as an hour or an hour and a half; along with his pyrexia it would still be truthful to say that there had been enough shock to produce anoxia and the changes subsequent to this.

DR. REINHARD: Dr. Harrington, please discuss briefly the pathogenesis of this patient's pathologic bleeding manifestations, particularly emphasizing, if you will, what effect shock has on blood coagulation, admitting that we have not established too easily that this patient truly had shock.

DR. WILLIAM HARRINGTON: The data that are available are fairly compatible with the coagulation defects seen in severe liver disease.

DR. REINHARD: What was the thrombocytopenia due to? Malamud stated that many of these patients that had heat stroke did have thrombocytopenia. What is the mechanism that has been suggested for this?

DR. HARRINGTON: I have doubts about the suggested mechanism, which is the effects of heat on megakaryocytes. Megakaryocytes are supposed to "burn up" in the marrow.

DR. REINHARD: I certainly agree with Dr. Harrington that that was not the factor which contributed to this patient's bleeding.

DR. MENDELOFF: In the same article those authors pointed out that the prothrombin times were usually normal in these patients. The liver was less prominently involved in this syndrome than other organs, although it is true that there were a few patients who were jaundiced. Pathologically the liver showed only centrolobular necrosis and in a few of these cases it was one of the less importantly involved

organs. These findings seem to me to point definitely away from hyperpyrexia as the sole cause of this man's disease. There is one other suggestion I would like to make. This man may have begun his hepatitis five or six weeks before the race, so that he may have been one of those people who have a prolonged anicteric period before coming down with a fulminant hepatitis. This is not the typical fulminant hepatitis occurring within ten days of onset of symptoms, but the less common disease in which rather nondescript or misleading symptoms for several weeks may make one think of some other disease, and then suddenly icterus, bleeding and neurologic symptoms develop after some incident or other; such patients have uniformly suffered a fatal course, although not always a rapid one, and it is possible that the race this patient ran may have been one of the factors which brought his disease to a disastrous end. This is a much less common disease form than the usual fulminant hepatitis, but it is a possibility here.

DR. REINHARD: Dr. Moore, what was the appearance of the megakaryocytes in his bone marrow?

DR. CARL V MOORE: None of the megakaryocytes had any evidence of platelet formation around the periphery. It is unfortunate that we do not have a platelet count on this man after June 22nd because it is certainly possible that his platelets might have been further depressed. I did not, however, see the quantitative changes in the nuclei or the cytoplasm of the megakaryocytes which are described in the article to which all of us have been referring. However, I would like to say a word about the prothrombin time. In the days when fever therapy was much more commonly used, particularly the so-called Kettering hypertherm box, it was noted that those patients sometimes had a reduction in prothrombin percentage. Dr. Doan studied this carefully and found that in his experimental animals and in patients exposed to high temperatures there was a lengthening of the prothrombin time which would sometimes persist for days. The prothrombin values were low in some of those patients Malamud described, and many of them also had increased bleeding times such as this man had. The authors had no explanation for the prolonged bleeding time except that it might have been due to hypoxia of the capillaries.

DR. REINHARD: Dr. Daughaday, one of the most remarkable features in this case was the profound hypoglycemia that was detected on the fourth hospital day. On June 18th this patient received 1,000 ml. of 5 per cent glucose in normal saline. On the following day the patient received another 1,000 ml. of 5 per cent glucose. On June 20th the patient received 500 ml. of 5 per cent glucose and on the morning of the 21st the patient's blood sugar was found to be 6 mg. per cent. At this time he had no symptoms of hypoglycemia. He was not unconscious. He was then given 100 gm. of glucose during the day, part of it in Ringer's solution and part of it in normal saline. At 7 P.M. that evening another blood sugar examination was reported as 12 mg. per cent. Would you discuss this?

DR. WILLIAM DAUGHADAY: The first thing of which we want to assure ourselves is the care and accuracy with which the determinations were done. When the laboratory technicians saw this amazing value in the presence of perfectly normal blood sugars from other patients, the possibility that some technical error had been made was thought of, and the determination was repeated with essentially the same results. Our blood sugars are done by the Somogyi-Hartman technic, in which the non-glucose reducing substances, amounting to 20 or 30 mg. per cent, are removed from the precipitate. In many severe insulin reactions this technic demonstrates that there is essentially no measurable blood glucose. These determinations were done carefully by a reliable method, so that there is no reasonable doubt that this man was profoundly hypoglycemic. The mechanism of hypoglycemia in this case was probably that of profound hepatic degeneration. Hypoglycemia in liver disease is a very fickle and unpredictable manifestation. One of the earliest results following hepatectomy in dogs observed by Mann was a progressive fall in the blood sugar; the dogs had to receive intravenous glucose continually to maintain their blood sugar. This individual was not releasing glucose properly from the liver, due to marked cellular destruction of the enzymatic factors involved, whether impaired gluconeogenesis or impaired glycogenolysis. Hypoglycemia in liver disease does not correlate with the usual liver function tests. Some of the most marked cases of hypoglycemia have been associated with cases of cholangitis with relatively negligible signs of parenchymal disease. Mellinkoff and Tumulty[3] have emphasized this

[3] MELLINKOFF, S. M. and TUMULTY, P. A. Hepatic hypoglycemia. *New England J. Med.*, 247: 745, 1952.

point. The failure of this man to respond to intravenous glucose is a little hard to explain. The correlation between blood sugar and symptoms is also quite erratic. Many diabetic patients may have symptoms of hypoglycemia with rather high blood sugar levels and others may not ha.e them at extremely low blood sugar levels. The rapidity of the fall of the blood sugar is considered an important factor, and the metabolism of the brain at that time is another important factor.

DR. REINHARD: Dr. Sherry would you discuss this patient's renal lesion? He had albuminuria and casts on several examinations. Azotemia was first noted on the fifth hospital day and progressed to levels of 144 mg. per cent nonprotein nitrogen on the eighth hospital day. Hematuria was first observed on the fifth hospital day. The inlying catheter was not inserted until the sixth hospital day. Furthermore, he had a low carbon-dioxide combining power during the first four or five days in the hospital, which then rose during the last four or five to more normal levels. What was the nature of his renal lesion?

DR. SOL SHERRY: These findings would probably fit best into the category of acute tubular necrosis. One would perhaps tend to relate this to the initial shocking episode, but the fact that this patient responded well after initial therapy and had a good urine output would not fit very well with that. One wonders what other factors might have contributed. We do have the evidence for severe acute hepatic necrosis, which raises the question of that ill defined entity, the hepatorenal syndrome. Whatever the factors are, at the time of the patient's death he did suffer from severe acute tubular necrosis and then progressive uremia developed. In addition, I would like to mention one factor that does not have to do with the renal disease but should be considered in relation to the bleeding that this patient exhibited: in patients with acute hepatic necrosis following phosphorus poisoning the blood fibrinogen levels drop very precipitously on about the second or third day. It might very well be that this individual had a very low fibrinogen level.

DR. REINHARD: With regard to the low carbon-dioxide combining power, this may not have been renal in origin, because it is very common in heat stroke. This has been attributed to alkalosis due to hyperventilation. We barely have time to discuss the neurologic manifestations this patient exhibited. Dr. Levy, what was going on in the nervous system here?

DR. IRWIN LEVY: The changes at the onset were probably not those of so-called heat stroke, but rather those of dehydration. I would expect what happened subsequently to be secondary to the rest of the illness, which I believe was not entirely due to heat.

DR. REINHARD: Now the final house staff diagnoses were (1) heat prostration and (2) acute diffuse hepatic necrosis due to unknown cause. I believe also that this patient had what I would prefer to call heat stroke, although I cannot be dogmatic about this. I am disturbed by the absence of a more marked hyperpyrexia, and by the absence of a more profound hypotension, but I believe that I would be inclined to say this patient's whole series of events was attributable to heat stroke.

PATHOLOGIC DISCUSSION

DR. W. STANLEY HARTROFT: Petechiae were present over the thorax of this well developed and nourished young man; periorbital ecchymoses and edema of the lower extremities and scrotum were present. Pleura, pericardium, heart, retroperitoneal tissues, peritoneum and renal pelves were covered with petechial hemorrhages. The left thoracic cavity contained 250 ml. of a dark yellow fluid, and the lower lobe of the corresponding lung was atelectatic. Volume of ascitic fluid was 950 ml. The most striking changes visible on gross examination involved liver and kidneys. The liver (Fig. 1) weighed 1,440 gm. and its wrinkled capsule suggested a recent decrease in size. Centrolobular regions were depressed and congested, while tissue about portal triads was soft and yellow. The capsules of the kidneys (combined weight 410 gm.) stripped readily, revealing a bile-stained parenchyma. The swollen cortices bulged on incision. The medullae were prominently congested. Other viscera did not appear unusual except for evidences of a slight degree of pulmonic congestion and edema. A few petechiae were present in the left temporal region of the cerebral cortex.

Extensive parenchymal necrosis is evident in microsections of the liver. The lesions are more advanced in samples from the left lobe than in those from the right. (Figs. 2 and 3.) In severely affected areas seas of necrotic tissue lap islets of surviving parenchyma that surround portal triads.

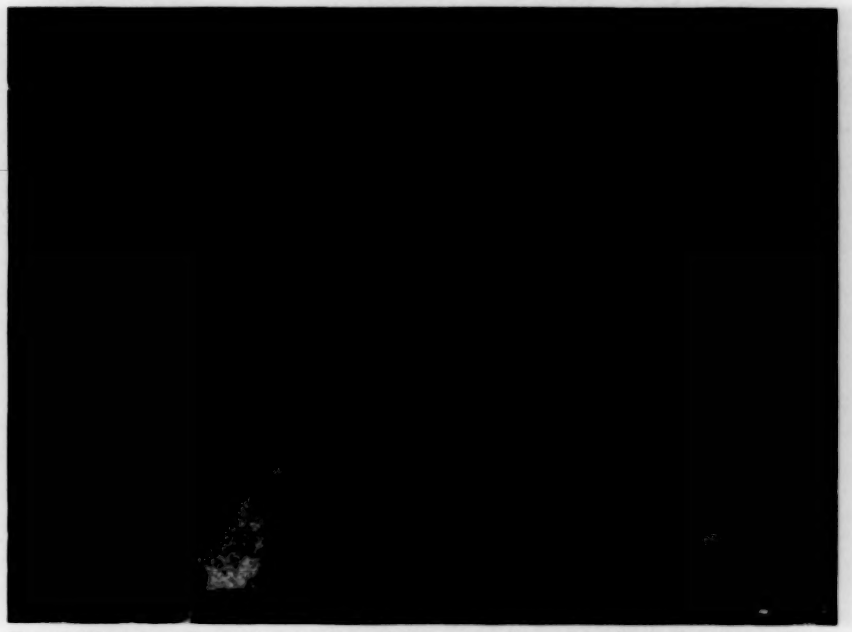

FIG. 1. Slightly enlarged gross view of the cut surface of the liver showing collapse and congestion of the central areas and soft yellow tissue about the portal spaces.

Parenchyma has been selected by the necrotic process, because in sections stained for reticulin, the stroma appears almost intact everywhere. (Fig. 4.) In the regions of portal triads (Fig. 5) additional features are noted: a moderate degree of infiltration of portal triads by small round cells, vacuolar degeneration of some hepatic cells (Fig. 6) and proliferation of pseudocholangioles. The vacuoles illustrated do not contain stainable lipid or glycogen and therefore are, by exclusion, probably representative of hydropic change.

A variety of interesting pigments are found in this liver. Iron is demonstrable within macrophages and multinucleated cells in the necrotic areas. Clumps of ceroid pigment (paraffin sections stained with Oil Red O) are present in necrotic areas, Kupffer's cells and in some surviving parenchymal cells. Bile pigment is present in degenerated hepatic cells and also as inspissated casts within bile canaliculi.

Many of the smaller branches of the hepatic artery contain large amounts of stainable fat distributed throughout every layer of their walls. (Fig. 7.) This arteriolar change is unique for the liver because it cannot be demonstrated in sections of the other viscera. Distal convoluted tubules (Fig. 8), in which there are prominent bile-stained casts and masses of necrotic cells, appear degenerated in renal microsections. Only a few rather insignificant heme casts are present within tubules. The changes of lower nephron nephrosis are, therefore, demonstrable, but only to slight degree.

Numerous microsections of the brain were examined. Shrunken and pyknotic cells are present within the dentate nuclei of the cerebellum, but there is no evidence of inflammation or more complete necrosis in the various nuclei or cortical areas. These changes in the neurons of the dentate nuclei are apparently of only recent origin.

It is my conclusion that this patient may have been the victim of some agent, possibly viral, that produces centrolobular necrosis of the liver. There are many reports of the pathologic findings in viral hepatitis, but only a few, including the article by Malamud, Haymaker and Custer, describe hepatic lesions in heat stroke. Centrolobular hepatic necrosis of variable extent occurred in one-fourth to one-half of their cases. Jaundice was present in only three of twenty-seven cases. But the severity of involvement of the left hepatic lobe compared to the right, the character of the portal inflammatory exudate, pseudocholangitic proliferation, bile plugs, deposits of ceroid and hemosiderin pigments and hydropic degeneration of hepatic cells, are considered by many as characteristic of the liver in viral hepatitis. Furthermore, extensive changes in the brain are a prominent feature in victims of heat stroke,

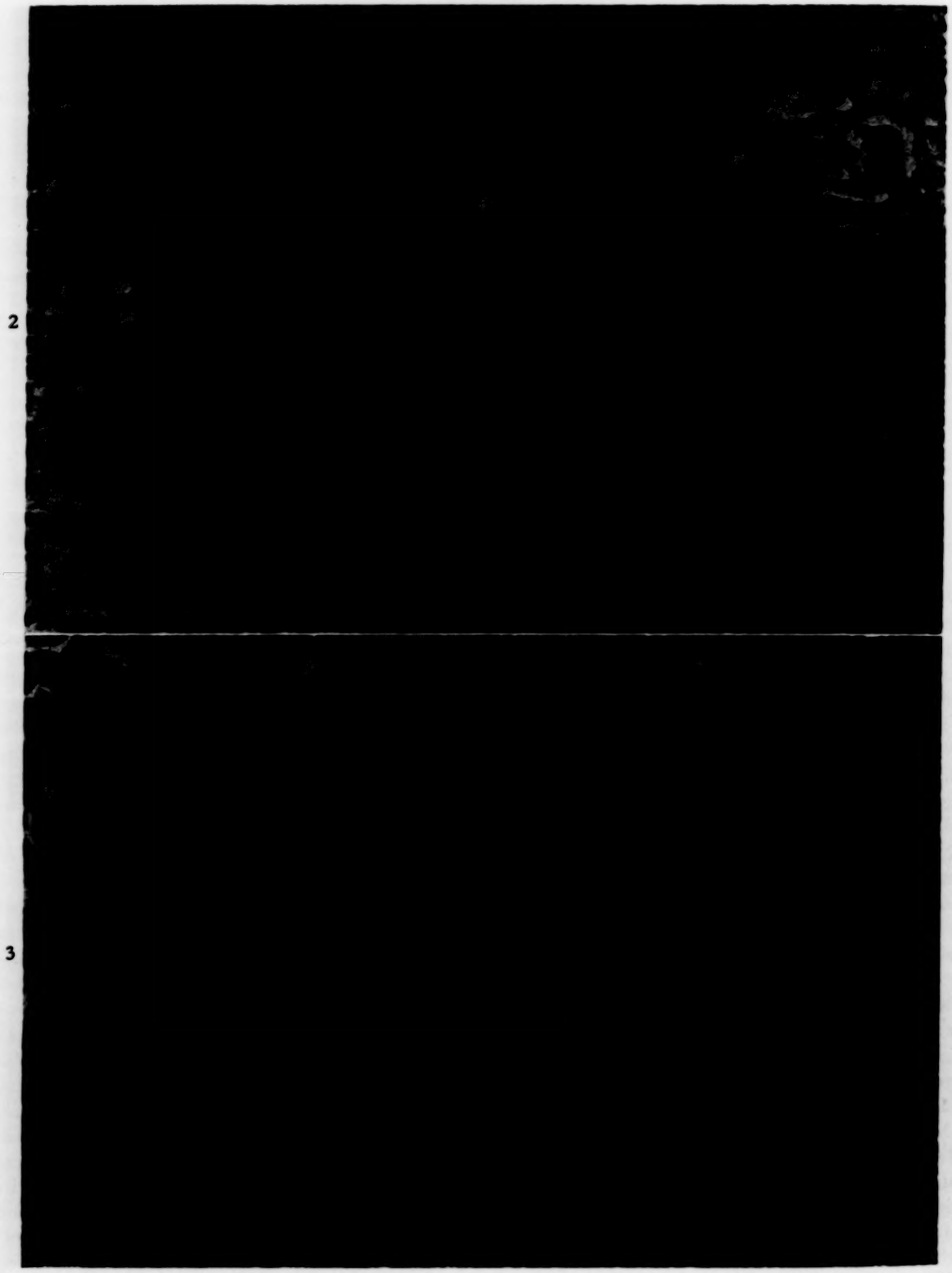

FIG. 2. Section of the left lobe of the liver with complete necrosis of the parenchyma except for small halves of surviving cells about terminal portal triads.

FIG. 3. Right lobe of the liver with the same qualitative type of change seen in Figure 2, but of considerably less intensity.

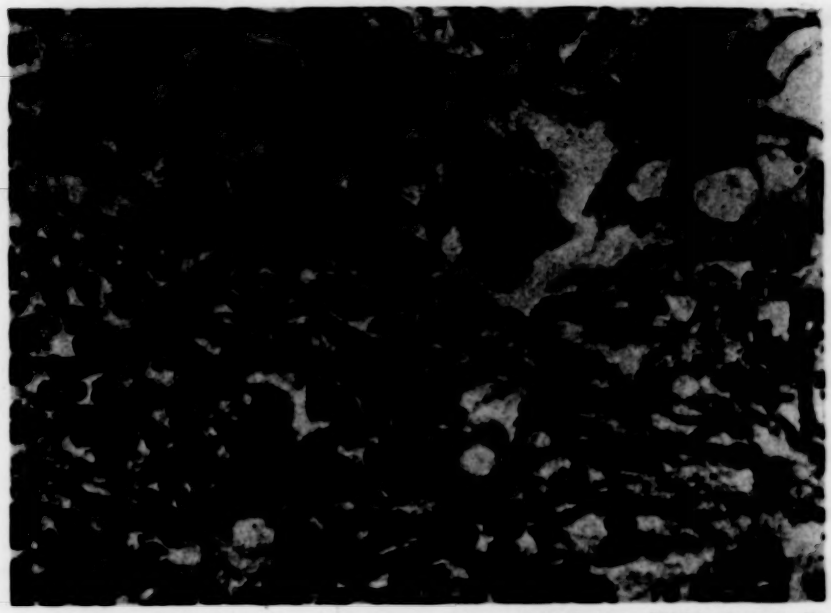

FIG. 4. Reticulin is little altered in many portions of the lesions (Wilder's reticulin stain).

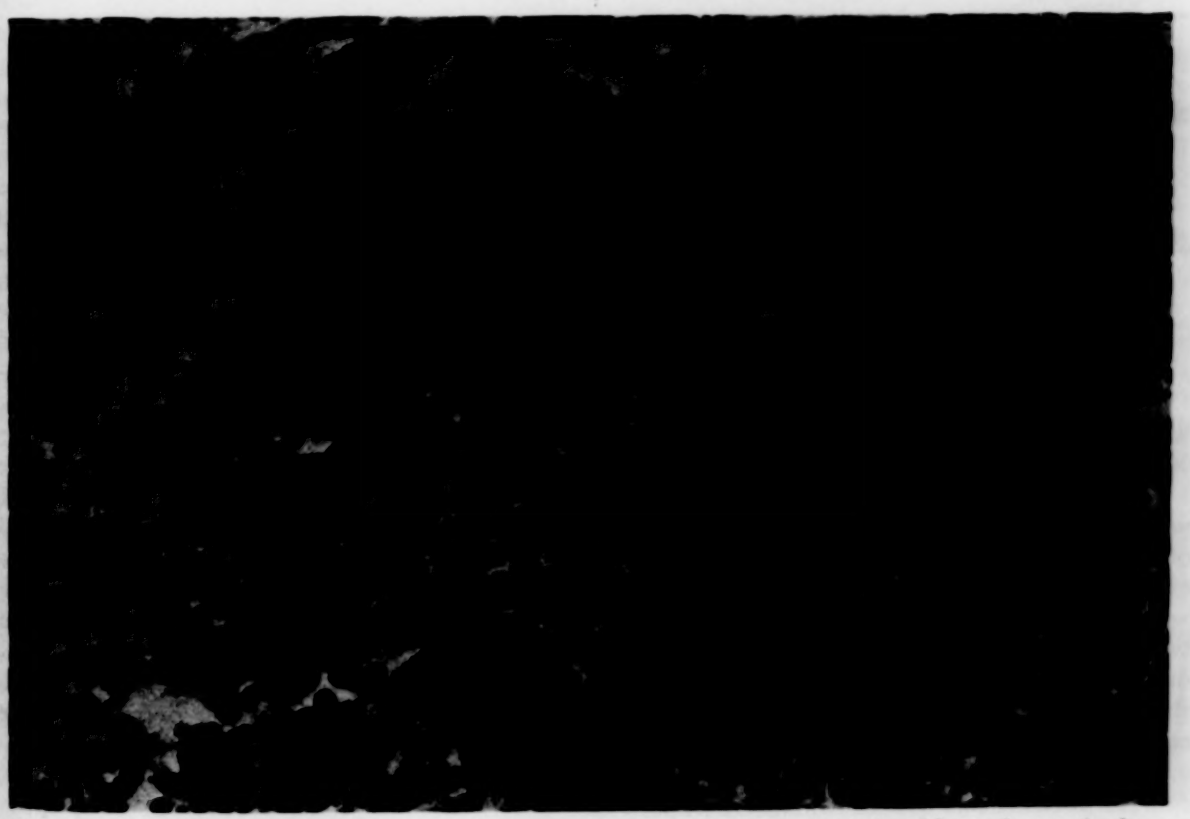

FIG. 5. Portal triad in the liver exhibits extensive infiltration, formation of pseudocholangioles and necrosis of surrounding hepatic parenchyma.

6 7

FIG. 6. Vacuolated and degenerating hepatic cell at the border of the necrosis.

FIG. 7. An arteriole in a portal triad with extensive deposition of stainable fat in its walls. The fat appears black in the photograph of the Oil Red O stain on frozen section.

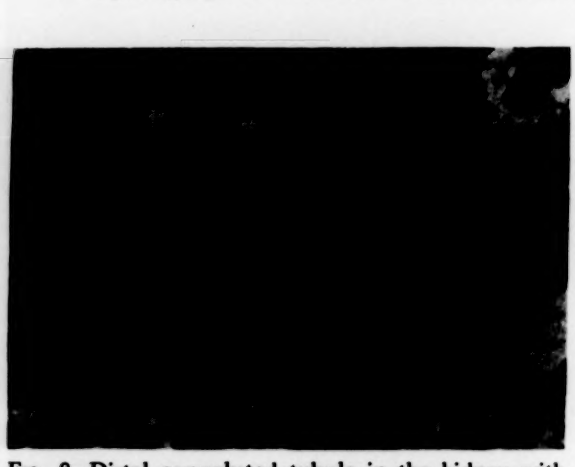

FIG. 8. Distal convoluted tubule in the kidney with degeneration of the epithelium and a large irregular, bile-stained mass of debris within its lumen.

along with cardiac and adrenal necrosis. Absence of significant cerebral, cardiac and adrenal lesions in the case under review and the presence of rather characteristic architectural and cytologic hepatic changes cited previously strongly suggest that this man died of hepatitis of viral origin that had undergone a fulminating exacerbation induced by heat exhaustion.

DR. SHANK: The pathologic findings seem to support the interpretation that this was predominantly a viral infectious process involving the liver that may have been influenced in its course by excessive exercise and heat. There are several considerations in this interpretation that can be drawn from our knowledge of experimental hepatic damage in animals and some of the epidemiologic studies of fulminant and fatal hepatitis during the war. In dietary necrosis of the liver, if one lowers the environmental temperature, it is more difficult to induce the lesion; so it seems quite likely that heat or high environmental temperature does contribute to hepatic necrosis. That is confirmed in an indirect manner in the classic study of Lucke[4] on hepatitis in the army. The peak incidence of death from this disease occurred in the heat of the summer. This has also been quite true in our clinical experience in that fatal cases of acute hepatic necrosis have occurred almost uniformly in the months of July, August or September. One troublesome feature of this case was the death following convulsions. Convulsions are uncommon in fulminant hepatitis, but they do occur, and the other features of the ten-day course seem to be quite compatible with those of fatal hepatitis. It should probably also be mentioned that the cases described by Malamud, Haymaker and Custer were derived from the same army population in which there were large numbers of cases of viral hepatitis. It might therefore be suggested that the occasional case described by them with extensive hepatic necrosis might have represented the coexistence of viral hepatitis and an exposure to excessive heat.

Final Anatomic Diagnoses: Massive hepatic necrosis compatible with viral hepatitis; lower nephron nephrosis; generalized petechiae.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

[4] LUCKE, B. Pathology of fatal epidemic hepatitis. *Am. J. Path.*, 20: 471–594, 1944.

Case Reports

Chloroma and Chloroleukemia*

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CHLOROMA is a green-colored tumor comprised of primitive white blood cells that usually involves the subperiosteal region of bone. It was originally described as forming large deposits in the ocular orbit and associated with a disorder of the blood-forming system manifesting itself as acute myelogenous or monocytic leukemia.

CASE REPORT

S. O., a twenty-one year old Negro man, came to the Admitting Department of the Boston City Hospital with a complaint of a painful swollen jaw. Five days prior to this the lower left third molar tooth had been extracted elsewhere because of local pain. There was much postoperative bleeding so he returned to his dentist the next day and the socket was packed. Pain and swelling progressed and he presented himself with extreme swelling of the left side of his face and submaxillary area. He had had dizzy spells causing fainting for two or three weeks. His past history revealed the usual childhood diseases. He had been in the Boston City Hospital five months before with a peritonsillar abscess, and in another hospital shortly thereafter for a tonsillectomy. The Boston City Hospital records showed a leukocyte count of 7,800 cells/cu. mm. at that time. The family history was negative. Mother, father, five sisters and four brothers were all in good health.

At the time of entry his temperature was 104°F., pulse 120, respirations 20. He was conscious, the left side of his face was swollen, the breath was fetid and there was a grayish membrane over the tooth socket. There was marked cervical lymphadenopathy. The remainder of the physical examination was negative. He was given 100,000 units of penicillin intramuscularly and 200,000 units thereafter every four hours. Sulfadiazine, 2.0 gm., followed by 1 gm. every four hours, was started the following day. The patient did not respond, his temperature rising to 105°F., on the second day after admission. He became lethargic and developed respiratory distress and cyanosis apparently from tracheal obstruction that was unrelieved by tracheotomy. Death was respiratory.

Blood studies carried out on oxalated blood after death revealed a leukocyte count of 130,000/cu. mm., hemoglobin 4.2 gm., and a red blood cell count of 1.45 million/cu. mm. The corrected erythrocyte sedimentation rate was 68 mm. per hour, the hematocrit was 12, the buffy coat was 10 and the icterus index was 2. Smears showed the predominant cell to be an early monocyte. Peroxidase stains made ten days later were negative.

Autopsy was performed twenty hours postmortem. The body was that of a very well developed and well nourished young Negro adult male. Rigor prevented adequate examination of the oral cavity but the gums and cheek around the extraction site were necrotic and hemorrhagic. There were multiple 1 cm. cervical nodes. The axillary and inguinal nodes were grossly enlarged. There was a 1 by 1 cm. tracheotomy opening from which exuded red frothy material; the subcutaneous tissues of the left side of the neck were slightly edematous and indurated but were not crepitant. There were no ecchymoses or petechiae. The mesenteric nodes were 1 to 3 cm. in diameter and were a bright chartreuse on section, the color fading soon after section. The appendix was a bright green. The surfaces of the lungs were covered with 3 to 5 mm. hemorrhages, old and new. The left pleural cavity contained 300 cc. and the right 150 cc. of clear green-amber fluid. There were 3 to 5 mm. hemorrhages over the pericardial surfaces. The heart weighed 400 gm. and was not remarkable. The currant jelly clot had a green

* From the Mallory Institute of Pathology, Boston City Hospital, Boston, Mass.

sheen. The tracheobronchial nodes were 2 by 3 cm., firm, olive green in color, and several had fibrotic or caseous centers.

The spleen weighed 220 gm. and contained a 2 by 3 by 3 cm. recent infarct. The cut surface was a dark green color that faded in one to two minutes. The stomach contained thin, dark blood and the wall was covered with petechial hemorrhages. The pancreas was negative. The liver weighed 2,680 gm. It was large, pale, and the capsule was smooth and glistening. The parenchyma had a distinctly green hue which was more marked in the connective tissue stroma. There was a 2 cm. poorly demarcated stellate green area. The kidneys had a smooth surface and were normal in appearance. The bladder contained several hundred cubic centimeters of clear, straw-colored urine. The left testicle was free in the abdominal cavity at the internal ring of the inguinal canal. There were many large 3.5 by 2.5 by 2.5 cm. bright green retropharyngeal lymph nodes. Several temporoparietal subarachnoid hemorrhages were present.

The surfaces of the brain were quite flat; there was a considerable quantity of bright red clotted blood in the subarachnoid space over the left cerebral hemisphere. In a horizontal section through the hemispheres several large hemorrhages were seen in the left hemisphere. These were situated in the central white matter and extended through the cortex to the meninges. In places, the large hemorrhages seemed composed of smaller ones. There were other small hemorrhages in the genu and splenium of the corpus callosum.

The sphenoid sinus contained green material that on smear consisted of immature white blood cells. The marrow of the vertebral bodies was a dark grass-green that faded quickly. The femoral marrow was hyperplastic, a dark red in color with a slight greenish hue.

Cultures from the mediastinum, spleen, lungs, sphenoid sinus and the tracheotomy all showed a heavy pure growth of hemolytic staphylococcus aureus. The green color of the marrow, spleen and nodes faded but could be restored by hyposulfite for several days. Thereafter this agent, as well as hydrogen peroxide, was not effective.

On microscopic examination, the heart muscle and vessels were not remarkable. The vessels and capillaries were engorged and contained nucleated blood cells, mostly leukemic cells. They were in the capillaries between the muscle fibers and occasionally occurred in small extravascular foci. In the lungs, the alveoli were filled with pink granular exudate, no inflammation. The capillaries of the alveoli were filled with the mononuclear cells seen in all vessels. The spleen was very cellular; there were few lymph follicles. The pulp was filled with leukemic cells. The architecture of the liver was preserved, with slight congestion in the center of the lobules. There was extensive portal leukemic infiltration; the sinusoids contained many such cells. The kidneys showed no abnormalities. The appendix showed a heavy infiltration of mucosa and adventitia and moderate infiltration of muscularis with the leukemic cells. The thyroid was not remarkable. The adrenals showed small leukemic foci but were otherwise normal. The diaphragm, stomach, intestine and skin all showed leukemic infiltrations. The prostate was not remarkable.

The lymph nodes all showed lack of the usual architecture. There was extensive infiltration by the leukemic cells and there were numerous rubriblasts. The femoral bone marrow had large solid areas of fat-free hematopoiesis. Rib, sternum and vertebrae all showed hyperplastic marrow. Large mononuclear cells overshadowed all other forms. These were poorly preserved but were thought to be monoblasts. There were numerous nucleated red cells but almost no remaining islands of pro-rubriblasts. The usual architecture was lost.

Hemolytic staphylococcus aureus was cultured from the spleen, mediastinum, lungs, sphenoid sinus and tracheotomy site.

DISCUSSION

These green tumors were first described by Allen Burns[1] in 1823. Other similar cases were reported by Balfour[2] in 1835 and by Durand-Fardel[3] in 1836. King,[4] however, was apparently the one to apply the term chloroma to these growths in the case reported by him in 1853. Aran[5] considered it a "green cancer" or a periosteal growth of a special color. Virchow thought it was a sarcoma. This concept was superseded by that of von Recklinghausen[6] and George Dock,[7] who showed the association of chloroma and acute leukemia. Dock collected sixteen cases in 1893 in which he noted the leukemic condition. He considered the large mononuclear cells to be large lymphocytes, as had all previous authors. With Warthin[8] he later summarized twenty-one cases collected between

1893 and 1904. The first cases reported as myelogenous leukemia were those of Turk[9] in 1903, Klein and Steinhaus[10] in 1904, and Sternberg[11] in 1905. Since that time there has been a steady increase in such cases reported.

Brannon[12] added fifty-six cases in 1926 and at that time considered that the cells in all of the well studied cases were proved to belong to the myeloid series. He noted that F. B. Mallory[13] was the only textbook author to consider chloroma as occurring with myelogenous leukemia. Kandel[14] listed the available cases from 1926 to 1936. The unquestionable cases totaled forty-six for this period; forty were obviously of myelogenous nature and in six the cells were peroxidase-negative and considered to be lymphocytic. Hartz and Van der Sar[15] tabulated fifteen more cases between 1936 and 1942, all of which were considered to be a variant of myelogenous leukemia. This brought the total summarized cases up to 190 but many of these were from the old literature and are not acceptable in evidence as to the origin of the tumor cell. The difficulty of identifying an early blast form of leukocyte is obvious, and the absence of peroxidase-positive granules is not conclusive proof that the cells are lymphocytic. Further, it has been pointed out by Burgess[16] in his report of a case from this laboratory that chloroma has never been seen in association with mature small-celled lymphatic leukemia. This should be considered as weighty evidence against the lymphatic origin of the tumor. In the case of Klein and Steinhaus[10] it was noted that the chloroma involved the periosteum of the bones of the head and trunk, the kidney, prostate and femoral marrow but expressly did not involve any of the lymph nodes.

All cases reported in recent years have been considered to represent acute myelogenous, monocytic or undifferentiated stem cell leukemia.[17–21]

Clinically, the classical case of chloroma is one in which there is an orbital tumor, frequently causing marked exophthalmos, lymphadenopathy, and a rapidly developing severe anemia associated with acute myelogenous or monocytic leukemia. The disease usually attacks children and young adults. Two cases of leukemia with chloroma have been noted in the newborn. One is reported by Morrison[22] in a thirteen day old child, and he refers to another reported by Saxl. Actually, the tumors may involve any portion of the body. Except for the localized effects of the tumors in any organ, the symptoms are essentially those of acute or subacute leukemia, namely, pallor, weakness, weight loss, bone pain, necrotizing angina, stomatitis, bleeding and cerebral hemorrhages. The spleen may be enlarged. Pleural effusions are common. The green tissue is seen in the viscera, sometimes diffusely, at other times in circumscribed tumors. Mitoses have been pictured and the tumors have been considered by some of the earlier reporters to be locally invasive; in fact, they were considered to represent a sarcomatous disease. The number of circulating white cells varies as in all leukemias; Vidari's[23] case had a count of 372,000 cells per cu. mm. The cells may not flood into the peripheral blood and the picture presented may be that of an aleukemic leukemia, the diagnosis being made by the clinical picture and by bone marrow studies. Leukopenia has been reported as low as 310/cu. mm. by Strasser.[24] There may be involvement of numerous bones, the most frequent being those of the skull, sternum, ribs, vertebrae, paranasal sinuses and, not uncommonly, the long bones. The x-ray appearance of the osseous system in chloroma has been summarized by Kemp and Williams.[25] There may be periosteal new bone formation about the shafts of the long bones, mainly parallel to the cortex and medulla and irregular in appearance. These changes are not specific and may be seen in other forms of leukemia, congenital syphilitic osteoperiostitis, scurvy, Ewing's sarcoma, etc.

The cells comprising the tumors and the leukemic infiltrate in the viscera are generally described as myeloblasts, myelocytes or monocytes. The tumor cell is a large mononuclear cell with a round or indented nucleus and with abundant cytoplasm. There is usually little stroma in the tumor mass but there is a moderate vascular supply. Reticulin is not formed, tumor giant cells are not found and megakaryocytes are found only in the marrow. In the report of Rothschild[26] the skull was involved in 73 per cent of the cases. The tumor has been reported as extending to the myocardium, causing almost complete stricture of the pulmonary artery. The ovaries are a very common site, along with the paravertebral nodes and the vertebral periosteum. The tumor may invade the neural canal as reported in the case of Griffin and Brindley[27] in which a twenty-six year old woman had the usual signs and symptoms of leukemia plus paralysis and loss of sensation in the lower

extremities. At autopsy a large soft green tumor mass was found extradurally extending from D-9- to L-1. Aballi[28] and Foulon[29] each report a case with compression of the spine by chloromatous tissue in the spinal canal. Discrete tumor nodules in the central nervous system are not described. One case of Critchley and Greenfield[30] had a green infiltration of the infundibulum and choroid plexuses with leukemic cells, but extension to the white matter had not occurred. Krumbein's[31] patient had mastoiditis and showed signs suggesting thrombosis of the lateral sinus and meningitis. Mastoidectomy revealed green tumor in the air cells. Lewis[32] reports a similar case. There may be infiltration about the peripheral nerves that could explain the pain that is a common occurrence. As noted before, any site may be involved. Huber[33] and Simon[34] each reported a case with signs of a malignant tumor in the breast, and radical mastectomy. Involvement of the eyes and ears has been described by Edgerton;[17] even the sclerae[35] and cornea[1] may be green. He also gives an extensive reference list of 336 reported cases of chloroma, many of which are open to question or were poorly studied.

The etiology of chloroma is not known. Only one case has been associated with a toxic agent. That was in a thirty-three year old man, reported by Rachner,[36] who had been a vulcanizer for nineteen years with exposure to benzene.

The malady is inevitably fatal. The only evidence to the contrary consists of two cases. One is reported by Lecene;[37] it was a tumor of the humerus in a twenty-three year old man that had been under observation for eighteen months at the time of operation. No abnormalities were found in the blood and the diagnosis was made on the basis of the tumor's green color and its predominant cell which he thought was a non-granular myelocyte. There was no leukemia and the patient was reported as well one year later. Lecene died shortly thereafter and no subsequent follow-up report of this case by another author has been found. The other case is that of Washburn[38] which was first reported in 1930. He has since published a follow-up note[39] reporting a fifteen-year study, the child remaining well. In retrospect he considers the case doubtful and suggests the possibility that it was xanthoma. It would appear highly likely that Lecene's case was of a similar nature.

The identity of the green pigment is not known, although there is considerable speculation and a fair amount of information concerning it. Balfour[2] believed it was bilirubin and Dittrich[40] thought that it was the result of "premature putrifaction." Early authors suspected that it was due to the rapid destruction of red cells. Askanzy[41] found no relationship between the genesis of the pigment and the destruction of red blood cells. Instead, he found a similar color in pus regardless of the infective agent, as long as it was predominantly polymorphonuclear; lymphocytes gave no color. Similar studies have been made by Agner[42,43] in which he has isolated a verdoperoxidase from the leukocytes of empyema fluid. This is found only in cells of the myeloid series.

The statement that the pigment is a lipochrome and that it contains iron apparently originated with Chiari.[44] Later work by Dustin and Thomas,[45] Amano[46] and Noda[47] indicates that it is a porphyrin. The spectrographic studies of these various authors far from duplicate each other, however. Amano points out that, according to his studies, the quantity of cytochrome in tumor tissue varies inversely with the degree of malignancy. This, he finds, is not true in the case of chloromatous tissue. He also showed a carmine-red fluorescence of the tumor tissue under ultraviolet light. His conclusions were that the green color was due to a porphyrin that was intimately associated with cytochrome and that this was the product of anomalous cytochrome synthesis within the chloroma cells. Noda believed that it could be produced in neoplastic myeloid cells that were embryonal, and concluded that it could be explained by an anomaly of the combination of iron to porphyrin. Roussy et al.[48] also found that the tissue of rat chloroma contained a protoporphyrin and gave a red fluorescence. They did not think, however, that the substance giving this color was assimilated into the pigment that gave the tumor its characteristic green tint in ordinary light. Zeldenrust, Veer and Nota[49] concluded that the green color was due to protoporphyrin and refer to the similar findings of Thomas Brigwood. The usual tests for urinary porphyrins have been negative when made in the reported cases even when the urine was green in color.

Humble[50] extracted chloroma tissue and studied it spectroscopically. He believed that his studies suggested that the pigments were derived from hemoglobin and choleglobin. He noted the choleglobin in man can be produced only in exceptional circumstances but that, in theory, it

could be derived from hemoglobin, cytochrome or catalase, also possibly from peroxidase, and that hemoglobin can be converted into choleglobin *in vitro* with ascorbic acid or glutathione.

In view of the conflicting results of the studies of these various authors, the nature of the substance causing the green color is still controversial. Cytochrome is found in all tissues and porphyrins have been shown to be increased when large numbers of young red blood cells are present as the result of hemorrhage or untreated pernicious anemia. It is reasonable to postulate that there may be a disturbance in the respiratory pigments in such a rapidly progressive malignant disease. The evidence at hand points to no other or unusual substances in these tumors.

Not all of the tumors are green in color. The patient described by Rosenbaum[51] had myelogenous leukemia, green marrow, green tint to the liver and spleen, but a solitary white tumor nodule in the liver and a large white retroperitoneal mass. Rowe and Hirschboeck[52] reported a case in a ten year old boy with myelogenous leukemia, treated by x-ray, with white myelogenous tumors of the cranial bones, face and ribs. In the cases of Pagniez[53] and of Hirschfeld[54] each was treated by x-ray and each was found to have white tumors. Kemp and Williams have reported a case as chloroma in which myelogenous leukemia developed in an eighteen month old infant and there were white tumor masses of myeloid cells in the dura, over the vertebrae and over the spinal theca extending through the spnial foramina. Bonnin[55] also reports a case of monocytic leukemia in a forty-five year old man who was found to have white "chloroma-like" tumors in the mediastinum, liver and spleen. It seems, however, that the descriptive term chloroma should be reserved for the cases showing the green pigment, at least diffusely if not as discrete tumors.

It would appear that chloroma is associated with an acute phase of myelogenous or monocytic leukemia. The tumor is composed of primitive white blood cells, with supportive connective tissue, stroma and vessels. Various combinations appear: leukemia with green pigment with and without actual tumor masses and leukemia with rather typical myeloid tumors but without the green color. Four to six cases are now reported annually in the world literature. The total number noted by Edgerton in 1947 was 336. The identity of the pigment is not at all definite. Many authors think it belongs to the cytochrome-porphyrin group; no conclusive evidence has been submitted and evidence to date is contradictory. Cases such as the one presented herein may show the color disturbance but no true invasive tumor. These have usually been referred to as chloroleukemia. Burgess' conclusions are still valid in that the tumors to which the term chloroma is applied do not constitute a pathologic entity but represent part of the pathologic process in acute leukemia, namely, a disturbance in the cellular pigment giving the characteristic bright green color.

SUMMARY

1. A case of acute monocytic chloroleukemia is presented.

2. Chloroma is not a pathologic entity but a tumor, green in color, consisting of leukemia cells and associated with acute myelogenous or monocytic leukemia. The green leukemic infiltrates may be diffuse and there may be no true tumor formation.

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Subacute Thyroiditis*

Report of Two Cases

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EIGHTEEN cases of subacute thyroiditis treated with cortisone or ACTH have been reported in the literature in the past four years.[1–9] In the most recent article Hunter and Sheehan report three cases[9] and stress the fact that in all the reported cases, as well as their own, the result of treatment with these hormones has been uniformly excellent. There have been no reports of poor response to cortisone treatment.

During a six-month period two patients with subacute thyroiditis were seen in office practice. One had a dramatic response to cortisone; the other had no response to adequate dosage over a sufficient time interval.

CASE REPORTS

CASE I. This forty-one year old white woman was first seen on August 8, 1953, with the chief complaint of a sore throat for one week. This had started with a feeling of soreness in the throat, worse on the right side, with radiation to the teeth and right ear. Associated with this was general malaise, headache and easy fatigability. Initial examination revealed a blood pressure of 100/70 and was otherwise negative except for a tender, firm area in the right lobe of the thyroid. Sedimentation rate was 50 mm. in the first hour. Within the next three days the temperature had risen to 101°F. The pain in the throat and ear had increased, and the area of tenderness and swelling in the right lobe of the thyroid was more prominent. On August 12, 1953, the sedimentation rate was 90 mm., the basal metabolic rate was plus 6, and the blood count was normal. The patient was started on cortisone, 300 mg. the first day, 200 mg. the second day, 100 mg. the third day and thereafter. Within twelve hours there was complete disappearance of all symptoms, fever and tenderness. During the course of the next few months every time an attempt was made to reduce the daily dosage below 50 mg. there was a recurrence of the patient's symptoms. This was accompanied by reappearance of tenderness and swelling in the thyroid gland, gradually migrating to the isthmus and then to the left lobe. By the time the disease had run its course the whole gland had been involved. Each relapse was immediately controlled within hours by increasing the dose of cortisone. On November 5, 1953, a radioactive iodine tracer study revealed almost no uptake over the whole gland. On December 14, 1953, four months after the onset of the disease, cortisone was discontinued with no recurrence. She has been asymptomatic since.

CASE II. This twenty-nine year old white woman was first seen on January 15, 1954, with a chief complaint of sore throat and earache. Her illness had started one week before with sore throat and pain in the right ear, followed in a few days by headache, general malaise, nausea and fever up to 99.6°F. Examination revealed a blood pressure of 110/70, temperature of 100.2°F. and marked tenderness and slight swelling of the thyroid gland, more marked on the right. The remainder of the examination was normal. By the following day the pain in the throat became more severe, radiating to both ears. Examination revealed increased swelling and tenderness over the thyroid gland. Basal metabolic rate was plus 20, sedimentation rate 10 mm. in the first hour and blood count normal. The patient was started on cortisone, 300 mg. the first day, 200 mg. the second day, 100 mg. the third day and thereafter. She was seen several times during the following two weeks. There was no change in symptoms or signs on this regimen and by February 2, 1954, she began to show rounding of the face and increasing weight despite dietary salt restriction. The

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